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VOLUME 102 (10) — OCTOBER 1993

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ANNALS
OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

Official Organ of the
AMERICAN LARYNGOLOGICAL ASSOCIATION

TUSSOMETRY: AN OBJECTIVE ASSESSMENT OF VOCAL CORD FUNCTION

OUTCOME OF OPEN SURGICAL THERAPY FOR GLOTTIC CARCINOMA

TEFLON GRANULOMAS AND OVERINJECTION OF TEFLON

HAIR RELAXER INGESTION: A NEW TREND

GROWTH RATE OF ACOUSTIC NEUROMA EXPRESSED BY Ki-67 NUCLEAR ANTIGEN VERSUS SYMPTOM DURATION

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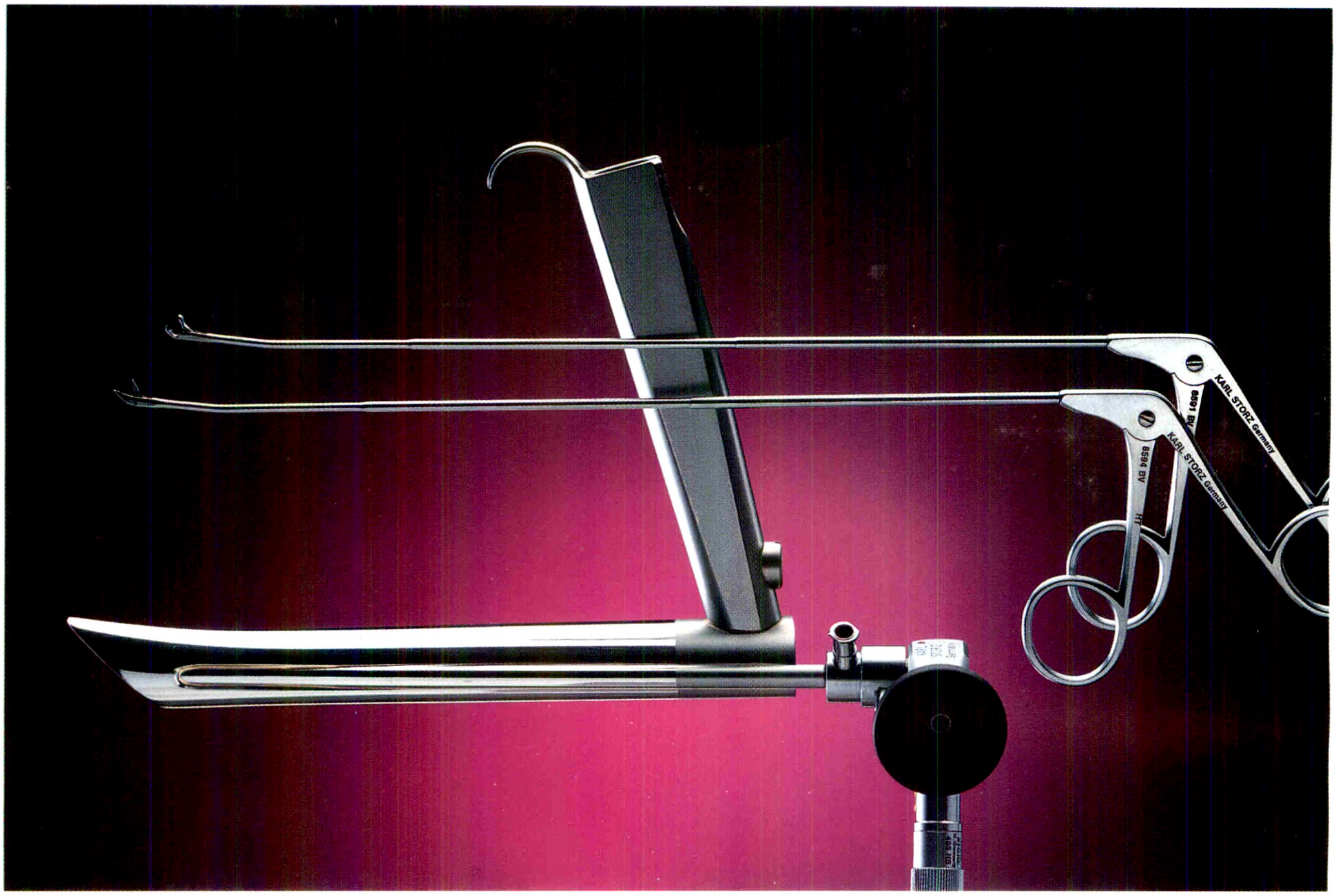

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TUSSOMETRY: AN OBJECTIVE ASSESSMENT OF VOCAL CORD FUNCTION

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A number of techniques have recently been developed for altering laryngeal function, including structural framework surgery, reinnervation procedures, augmentation of the vocal cords, electrical stimulation, and pharmacologic intervention. The application of such procedures to appropriate disorders would be facilitated by better objective measures of the outcome. This study describes the new technique of tussometry, which investigates the airflow pattern produced during coughing. The value of 1 parameter, peak value time, is shown by a study of 35 vocal cord palsies versus a control, and of 17 vocal cord palsies before and after augmentation, to be an accurate assessment of vocal cord position. The technique is independent of lung function parameters and intraoral pressures. It is truly objective, having an interobserver variation of 0%, and is eminently reproducible, with an intrasubject coefficient of variation of 3.1% to 5.7%. Tussometry is a rapid, noninvasive technique providing inexpensive objective assessment of vocal cord function in the office setting.

KEY WORDS — airflow, cough, tussometry, vocal cord function.

INTRODUCTION

A number of innovative techniques have recently been developed for improving laryngeal function, including structural framework surgery, reinnervation procedures, augmentation of the vocal cords, electrical stimulation, and pharmacologic intervention. The application of such procedures to appropriate disorders would be greatly facilitated by better objective measurements of the outcome.

The technique of tussometry, involving analysis of the airflow pattern produced during a single maximal-effort voluntary cough, has recently been developed and has been proposed as a possible method of objectively assessing laryngeal function.[1] The aim of this study was to investigate the role of vocal cord mobility and position in tussometry to determine if the technique has a role in laryngology.

MATERIALS AND METHODS

The technique of tussometry involves the measurement of airflow with a pneumotachograph system consisting of a modified anesthetic mask, a Gaeltec (Dunvegan, Isle of Skye, Scotland) flowmeter and flow transducer (model E9307), an analog

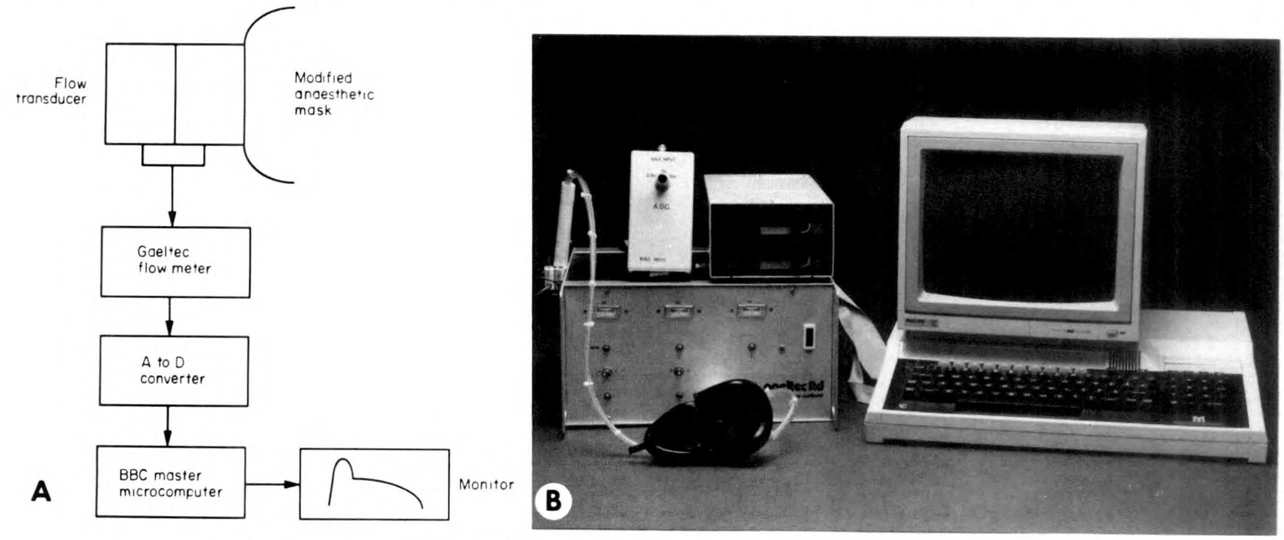

Fig 1. Tussometer. A) Diagram. B) Actual.

From the Department of Otorhinolaryngology, University Hospital, Nottingham (Murty, Bradley), and the Department of Medical Statistics, University of Newcastle upon Tyne, Newcastle upon Tyne (Kelly), England.

Presented at the meeting of the American Laryngological Association, Los Angeles, California, April 17-18, 1993.

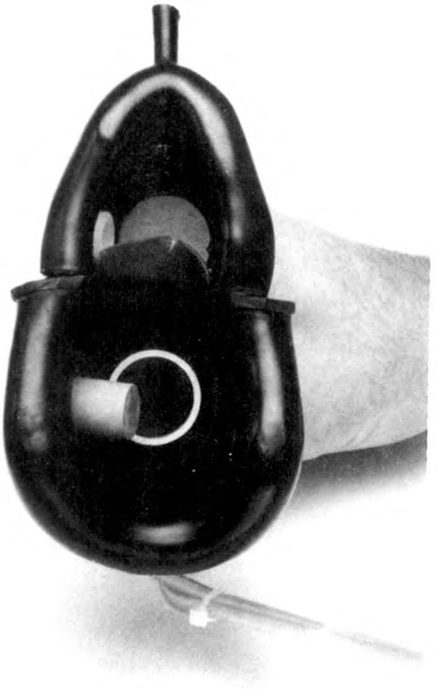

Fig 2. Modified anesthetic mask.

to digital converter, and a BBC Master Series microcomputer (Fig 1). The modified anesthetic mask (Fig 2) consists of the top half of a size 2 and the bottom half of a size 6 MIE standard anesthetic mask. A rubber partition and sealant were used to separate nasal flow from airflow. The flowmeter and transducer have a frequency response of 0 to 250 Hz, and the analog to digital converter has a digitalization voltage of 0 to 2.5 V, giving 255 levels.

The subject coughs into the modified anesthetic mask and the pressure differential across the mesh within the transducer is used to derive airflow. By means of the analog to digital converter and the BBC Master Series microcomputer, this is displayed in graph form.

The subject is seated in an upright position and the procedure is explained. Two coughs are taken to clear any excess mucus. A deep inspiration is then taken before the subject coughs as forcefully as possible into the mask. This the subject holds firmly over the nose and mouth, preventing any air leaks. Two practice attempts are permitted before readings are measured. The airflow pattern during a single maximal-effort voluntary cough is then recorded from 3 consecutive attempts.

Two parameters are recorded: the y- and x-axis values of the peak of the trace. The y-axis represents the airflow in liters per minute, and the value of the peak is designated the peak (P). The x-axis represents the time in milliseconds since the onset of the cough, and the value of the peak is designated the peak value time (PVT). Figure 3 shows a trace with a P value of 362 Lmin^{-1} and a PVT value of 45 milliseconds.

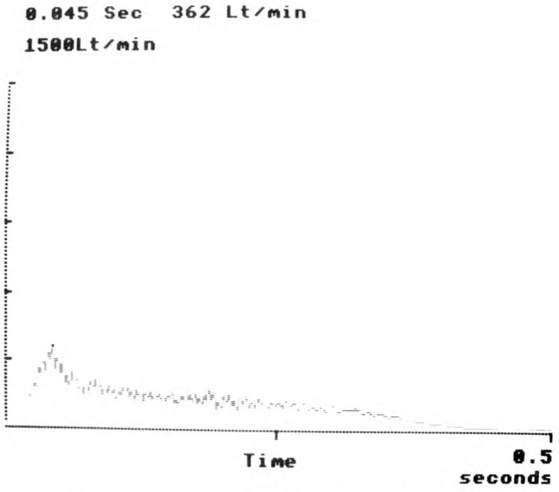

Fig 3. Tussometry trace showing peak of 362 Lmin^{-1} and peak value time of 45 milliseconds.

As the technique is effort-dependent, the "best" trace of the 3 recordings made was taken as being the truest. "Best" is defined as the trace with the lowest PVT value.

Vocal Cord Paralysis. Thirty-five patients with unilateral recurrent laryngeal nerve vocal cord paralysis confirmed by fiberoptic nasolaryngoscopy were studied. The underlying cause, time since onset, age, and sex of the subject are indicated (Table 1). For the purpose of this study the description of cord positions was confined to 2: the paramedian and the lateral (or cadaveric) position. All subjects tested had a vocal cord palsy in the lateral position. The control group consisted of 35 age- and sex-matched volunteers in whom history and clinical examination failed to demonstrate any disease of the nasal or upper aerodigestive tracts. None of the subjects tested was a smoker, and none was receiving an antitussive, bronchodilator, or bronchoconstrictor preparation.

The mean P and PVT values for both the vocal cord palsy and the control groups were compared by means of a paired *t* test, and confidence intervals (CIs) for the mean differences were calculated.

Vocal Cord Augmentation. Seventeen patients undergoing vocal cord augmentation were studied further. They were subjects 19 to 35 inclusive in Table 1. The P and PVT values were measured before and 48 hours after augmentation. At microlaryngoscopy under general anesthesia an amount of polytetrafluoroethylene sufficient to displace the cord to the midline was injected. This ranged from 0.2 to 0.6 mL. The success of augmentation was determined by

TABLE 1. CLINICAL DETAILS OF VOCAL CORD PALSY PATIENTS ASSESSED BY TUSSOMETRY

Subject	*Sex*	*Age (y)*	*Palsy Duration*	*Cause*	*P (Lmin^{-1})*	*PVT (msec)*
1	M	79	15 y	Thyroidectomy	309	102
2	F	56	6 wk	Bronchial cancer	121	76
3	M	62	18 mo	Idiopathic	508	45
4	F	75	15 mo	Aortic aneurysm	215	86
5	F	54	6 mo	Thyroidectomy	614	58
6	F	61	10 mo	Carotid surgery	256	63
7	M	69	13 y	Idiopathic	285	214
8	F	63	30 y	Thyroidectomy	110	48
9	F	24	2 mo	Subarachnoid hemorrhage	274	55
10	M	72	8 mo	Esophagectomy	725	86
11	F	72	3 mo	Malignant cervical node	168	74
12	M	49	13 mo	Thoracotomy	309	86
13	M	50	4 mo	Idiopathic	866	95
14	F	59	5 mo	Bronchial cancer	186	158
15	F	61	5 mo	Pneumonectomy	77	92
16	F	71	7 mo	Bronchial cancer	63	106
17	F	61	18 y	Radical neck dissection	133	69
18	M	62	2 mo	Lung metastasis	285	95
19	M	72	8 mo	Bronchial cancer	151	68
20	M	68	6 mo	Bronchial cancer	350	76
21	M	70	5 mo	Bronchial cancer	162	72
22	M	67	3 mo	Bronchial cancer	561	102
23	M	69	3 mo	Pneumonectomy	379	77
24	M	55	2 mo	Pneumonectomy	215	81
25	M	71	4 mo	Bronchial cancer	356	63
26	M	66	10 mo	Pneumonectomy	250	67
27	M	68	22 mo	Idiopathic	297	76
28	M	61	4 mo	Idiopathic	303	66
29	M	45	11 mo	Esophagectomy	473	69
30	F	76	4 mo	Idiopathic	174	66
31	M	61	5 mo	Bronchial cancer	626	97
32	M	58	4 mo	Bronchial cancer	584	71
33	M	66	18 mo	Bronchial cancer	168	70
34	F	42	11 mo	Cloward's procedure	250	77
35	M	68	30 mo	Pneumonectomy	338	59

P — peak, PVT — peak value time.

direct visual inspection of cord contact during recovery from anesthesia, and confirmed by indirect laryngoscopy and subject self-evaluation of the outcome 48 hours later. Membranous cord contact and an improvement in symptoms were achieved in all 17 cases.

The mean P and PVT values before and after augmentation were compared by means of a paired *t* test, and the CIs for the mean differences were calculated.

RESULTS

Vocal Cord Paralysis. The mean age for the vocal cord palsy group was 62.4 years (range 24 to 79), and that for the control group was 62.3 years (range 27 to 84). There were 22 men and 13 women in each group. The P and PVT values of the vocal cord palsy group are shown in Table 1, and those of the control group in Table 2.

The mean P was 318.3 Lmin^{-1} (range 110 to 866) for the vocal cord palsy group and 420.9 (range 110 to 1,083) for the control group (Fig 4A). The difference in means was 112.5 with a standard error (SE) of 320.5 (95% CI 2.4 to 222.7). The decrease in P value in the vocal cord palsy group is of borderline significance ($p = .04$).

The mean PVT for the vocal cord palsy group was 81.86 milliseconds (range 55 to 214), and for the control group, 28.6 (range 11 to 51; Fig 4B). The difference in means was 53.26 (SE = 5.42), from which a 95% CI for the difference in means can be calculated as 42.25 to 64.27. Hence, there is a significant increase ($p < .0001$) in the PVT value for the vocal cord palsy group.

Vocal Cord Augmentation. The mean age was 63.7 years (range 42 to 76), and there were 15 men and 2

TABLE 2. P AND PVT VALUES IN VOCAL CORD PALSY CONTROL GROUP

Control	*Sex*	*Age (y)*	*P* ($Lmin^{-1}$)	*PVT (msec)*
1	M	79	174	24
2	F	57	538	40
3	M	66	256	23
4	F	72	209	23
5	F	50	233	23
6	F	60	1,083	51
7	M	69	280	27
8	F	67	192	32
9	F	27	391	31
10	M	70	426	34
11	M	42	778	38
12	M	50	479	24
13	M	44	626	25
14	M	52	497	33
15	M	57	356	22
16	M	61	649	35
17	M	64	702	30
18	M	64	455	30
19	M	67	532	30
20	M	65	549	17
21	M	70	239	30
22	M	71	626	38
23	M	68	110	11
24	M	68	321	20
25	M	72	455	30
26	M	67	262	34
27	F	40	397	41
28	F	53	350	27
29	F	62	280	38
30	F	62	151	15
31	F	70	192	20
32	F	74	133	18
33	F	84	749	23
34	M	66	600	30
35	M	71	810	34

P — peak, PVT — peak value time.

TABLE 3. P AND PVT VALUES BEFORE AND AFTER AUGMENTATION

	Preaugmentation		*Postaugmentation*	
Subject	*P* ($Lmin^{-1}$)	*PVT (msec)*	*P* ($Lmin^{-1}$)	*PVT (msec)*
19	151	68	198	23
20	350	76	344	23
21	162	72	209	23
22	561	102	510	31
23	379	77	315	37
24	215	81	198	36
25	356	63	227	20
26	250	67	145	19
27	297	76	215	19
28	303	66	227	23
29	473	69	460	48
30	174	66	151	31
31	626	97	543	37
32	584	71	432	30
33	168	70	151	41
34	250	77	291	34
35	338	59	362	45

P — peak, PVT — peak value time.

women. The P and PVT values before and after augmentation are shown in Table 3.

The mean P preaugmentation was 330.7 $Lmin^{-1}$ (range 151 to 561), and that postaugmentation, 292.82 (range 145 to 543; Fig 5A). The difference in means was 38.8, with an SE of 14.8 (95% CI 7.5 to 70.1). The difference in P value following augmentation is significant ($p = .018$).

The mean PVT preaugmentation was 73.94 milliseconds (range 59 to 102), and that postaugmentation, 30.59 (range 19 to 48; Fig 5B). The difference in means was 43.4, with an SE of 3.3 (95% CI 36.3 to 50.4). The decrease in PVT value following augmentation is strongly significant ($p < .0001$).

DISCUSSION

Tussometry is a new, noninvasive technique in which the airflow waveform produced during a single maximal-effort voluntary cough is analyzed.[1] Reproducibility studies have demonstrated that the technique is truly objective, having an interobserver variation of 0%, and is eminently reproducible, with P and PVT being relatively constant physiologic param-

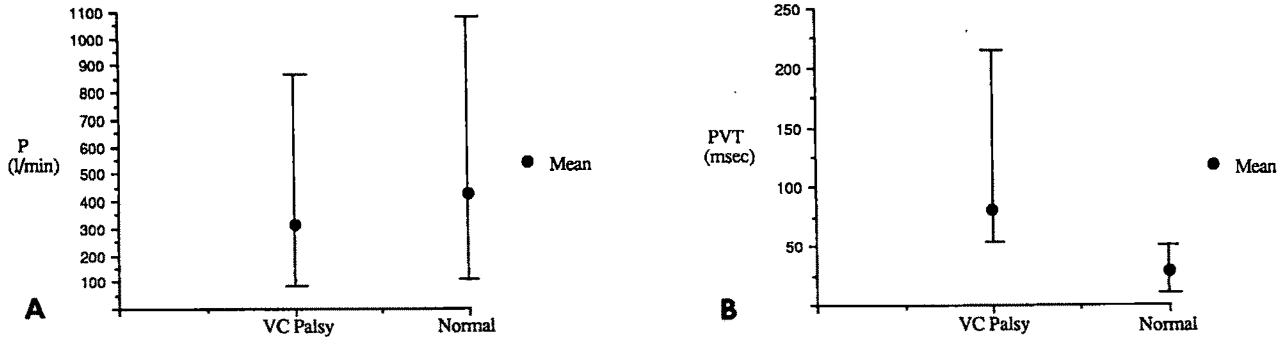

Fig 4. Comparison of vocal cord (VC) palsy group to control group. Filled circles — means, lines — ranges. A) Peak (P). B) Peak value time (PVT).

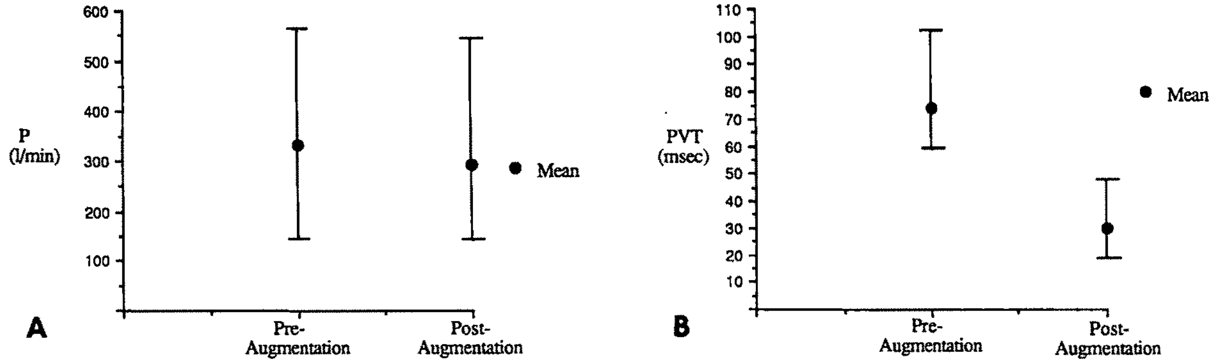

Fig 5. Comparison of patients before and after augmentation. Filled circles — means, lines — ranges. A) Peak (P). B) Peak value time (PVT).

eters — PVT being particularly reproducible, with a coefficient of variation of 3.1% to 5.7%.[2]

In this study the tussometric findings of subjects with a vocal cord palsy in the lateral position were compared to those of a control group. The reduction of P in the vocal cord palsy group was of borderline significance, but the PVT was significantly increased; PVT therefore appears to be a more promising measure of vocal cord function.

The increase in the PVT may have been due to either the lack of actual movement of the paralyzed cord or the lateral position of the cord. To investigate this question, subjects with a palsy were studied before and after augmentation. The PVT was found to significantly decrease as a result of augmentation. This suggested that it was the position of the cord, rather than the lack of movement, that produced the PVT increase.

The lower and upper respiratory tracts may theoretically influence the PVT value. Accordingly, the correlation of standard lung function parameters, maximal intraoral pressures, and PVT has been investigated.[3] The PVT proved to be independent of these variables and is therefore specifically a measure of laryngeal function.

In conclusion, therefore, the parameter PVT is a simple, rapid, reproducible, noninvasive objective measure of the position of the vocal cords. It may prove to be of benefit in the diagnosis and assessment of treatment of vocal cord disorders.

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FOURTH INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons will sponsor the Fourth International Conference on Head and Neck Cancer, to be held from July 28 to August 2, 1996, in Toronto, Canada. For further information, contact We Plan Meetings, Inc, Ruth C. Enquist, President, 1503 15th St NE, Rochester, MN 55906; telephone (507) 285-1523; fax (507) 281-8328.

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TEFLON GRANULOMAS AND OVERINJECTION OF TEFLON: A THERAPEUTIC CHALLENGE FOR THE OTORHINOLARYNGOLOGIST

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We have found that Teflon granulomas and the overinjection of Teflon with the resulting laryngeal dysfunction, although uncommon, present a challenge to the otorhinolaryngologist, due in large part to the inflammatory reaction to the injected Teflon. This report addresses the management of 16 patients (12 women and 4 men) treated surgically for symptoms secondary to Teflon granulomas or vocal folds that had been overinjected with Teflon. The presenting symptoms varied and included airway obstruction, cough, choking, swallowing difficulties, and dysphonia. In each case the granuloma and Teflon were removed endoscopically via a lateral cordotomy. A second procedure to address dysphonia due to vocal cord lateralization was frequently required and presents the challenge for the surgeon to select the appropriate procedure and time of intervention. The results of this retrospective review suggest that resolution of inflammatory changes and fibrosis subsequent to Teflon removal requires significant lengths of time and that thyroplasty techniques provide a means for medialization without reintroduction of the original inflammatory material.

KEY WORDS — granuloma, Teflon injection, thyroplasty, vocal cord.

Teflon injection is a well-established technique to medialize an immobile vocal cord with a low incidence of failure or complications.[1-3] Among the complications seen following Teflon injection, 1) dysphonia and airway obstruction associated with granulomas and 2) dysphonia associated with overinjection of Teflon. These are challenging to treat, because of the foreign body reaction associated with Teflon.[4-7] This inflammatory process presents difficulty for several reasons. First, the foreign body reaction and fibrosis make Teflon removal tedious and time-consuming. Second, the required dissection results in further violation of the vocal cord mass with subsequent scarring and fibrosis, further altering the vocal cord position and waveform. Finally, the resolution of this inflammatory process is variable and slow. The combination of scarring, fibrosis, and gradual resolution of the chronic inflammatory reaction makes it difficult to predict the final position and character of the vocal cord. Thus, the otorhinolaryngologist may be faced with the following dilemma: 1) Will intervention produce a deterioration in the patient's voice? 2) What is the best way to remove Teflon? and 3) How and when should the dysphonia be managed after Teflon removal?

This report describes a retrospective review of 16 patients managed with symptoms of dysphonia and/or airway obstruction secondary to Teflon granulomas or the overinjection of Teflon.

MATERIALS AND METHODS

The records of all patients treated surgically for the removal of Teflon following vocal cord injection were reviewed. Information recorded included sex, age, number of injections, time interval between the last injection and presentation for treatment, symptoms, and time interval between removal and procedures performed to address symptoms that developed subsequent to the removal of Teflon.

The removal of Teflon was undertaken laryngoscopically in all cases and performed via a lateral cordotomy. Some patients in the study had the Teflon removed by dissection with a carbon dioxide (CO_2) laser. However, other patients were treated with standard microsurgical instruments to avoid laser treatment of the vocal cords. Subsequent to Teflon removal, the patients were followed up at intermittent periods, and those who developed symptoms related to a lateralized or bowed vocal cord were subsequently treated with reinjection of Teflon or thyroplasty and arytenoid adduction techniques.

RESULTS

Sixteen patients (12 women and 4 men) presented to the otorhinolaryngology department at Mayo Clinic

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Presented at the meeting of the American Laryngological Association, Los Angeles, California, April 17-18, 1993.

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TABLE 1. VOCAL CORD DISORDERS PROMPTING TEFLON INJECTION

Diagnosis	*No. of Patients*	*No. Requiring Secondary Procedures After Teflon Removal*
Vocal cord paralysis		
Postoperative	6	2
Traumatic	2	1
Idiopathic	4	3
Mobile cords	4	3
Total	16	9

with symptoms of dysphonia and airway obstruction subsequent to Teflon injection. Thirteen patients presented with dysphonia alone, and 3 patients presented with dysphonia and airway obstruction secondary to a Teflon granuloma partially obstructing the glottic airway. Additional symptoms noted in a variety of patients included swallowing difficulties, choking, and cough. Table 1 presents the vocal cord disorders that prompted the Teflon injections and presents the number of patients who required a secondary procedure. Table 2 presents the age and sex of patients who underwent Teflon removal and as well presents the interval between the last injection (when multiple injections were performed) and the date of removal. Table 2 also presents the time interval between the removal of Teflon and the secondary procedure required for subsequent dysphonia.

Among the 16 patients who underwent Teflon removal, 5 (31%) required 2 procedures to adequately remove the Teflon and the associated inflammation. Two patients had Teflon granulomas of sufficient size to warrant a tracheotomy in conjunction with Teflon removal. Five of the 16 patients who underwent Teflon removal had received multiple Teflon injections in the involved vocal cord.

The type of secondary procedure employed to address the glottic insufficiency following Teflon removal varied and related to the individual surgeon's preference. One patient underwent reinjection of Teflon, and 1 patient had an arytenoid adduction alone. Five of the 9 patients who underwent secondary procedures had a type I thyroplasty. Two patients underwent a type I thyroplasty plus an arytenoid procedure, either an arytenoid adduction or an arytenoid fixation. All 16 patients were satisfied with their voice quality at the conclusion of treatment and at subsequent follow-up visits.

DISCUSSION

The reported incidence of complications and failure following Teflon injection is low, ranging from 2% to 10%.[1-3] Previous reports have addressed the proper technique of injection, the proper means of patient selection, and the limitations of Teflon injection. Few reports, however, address the management of the overinjection of Teflon or Teflon granulomas.[8,9] The management of dysphonia subsequent to Teflon removal has not been addressed and presents a challenge for the otorhinolaryngologist. With the recent development of laryngeal procedures such as thyroplasty and arytenoid adduction, the laryngeal surgeon can now address the dysphonia subsequent

TABLE 2. DATA RELATING TO TEFLON REMOVAL

Age	*Sex*	*Interval Between Injection and Removal**	*Month and Year Teflon Removed*	*CO2 Laser Used for Removal*	*Interval Between Teflon Removal and Secondary Procedure (mo)†*
29	F	11 y 1 mo	4/92	+	4
38	F	3 y 1 mo	2/88, 12/89	+	
41	M	5 y	11/90	+	10
45	F	18 y	8/91, 3/92	+	
45	F	10 y	11/84, 5/88	+	12
47	F	5 y 2 mo	8/91, 10/91	+	
52	F	6 y 7 mo	6/90	+	2
54	F	4 mo	8/90, 2/91	–	8
59	M	2 y	9/91	+	6
61	F	4 y 4 mo	2/85	–	
63	M	9 mo	7/91	–	5§
63	M	2 y	5/91	–	11
65	F	1 y 3 mo	11/81	–	
74	F	1y 11 mo	11/90	–	5
78	F	8 mo	3/84	–	
83	F	7 mo	10/82	–	
Average (mo)		55			6

*Interval from last injection to removal, if more than 1 injection.

†Interval from removal to first secondary procedure, if more than 1 required.

§Arytenoid adduction performed 5 months prior to Teflon removal (not included in calculating average).

to Teflon removal without reintroducing the original inflammatory material.

Very few reports discuss the techniques and considerations for Teflon removal. A recent report by Dedo[9] presents Teflon removal as a procedure in which a midline vocal cord is obtained by removing the appropriate amount of Teflon from a previously injected cord. In our experience, this was not accomplished in 56% (9 of 16) of our patients who had Teflon removed because of several factors. First, there is a significant but variable degree of chronic inflammation associated with Teflon. The time course associated with the development and resolution of this chronic inflammatory reaction is variable, as evidenced by the wide range of time intervals between injection and removal of Teflon. As revealed in Table 2, the interval between the patients' last Teflon injection and the removal of Teflon ranged from 4 months to 18 years, with a mean of 55 months. This range would suggest that a portion of these patients had a satisfactory voice for a significant length of time and that the development of dysphonia and airway obstruction is related to a persistent, expanding inflammatory reaction to the Teflon. Not only is the progression of the inflammatory reaction to Teflon variable, but the resolution of this inflammatory reaction is also variable, as evidenced by the interval range between Teflon removal and the need for subsequent vocal cord repositioning.

Another factor influencing the success of Teflon removal is the unlikelihood of finding a single mass of Teflon that one can selectively remove to adjust the position of the vocal cord. Typically, Teflon is interspersed piecemeal throughout the cord and intermixed with the chronic inflammatory reaction. The above considerations make it difficult to precisely remove the amount of Teflon and inflammatory material that will produce an accurately medialized vocal cord.

Two approaches are available in Teflon removal. One can attempt total removal or attempt to remove some Teflon, leaving an "adequate amount" for appropriate medialization of the vocal cord. First, it is difficult to assess the amount of Teflon that should or should not be removed to leave the cord in an appropriate position. It is even more difficult to predict the rate and extent of resolution of the inflammatory changes related to the Teflon. Finally, the subsequent fibrosis related to Teflon removal is delayed and further disables prediction of the final cord position. Therefore, deciding the appropriate amount of Teflon removal is not possible on a consistent basis — a conclusion based in part on our findings that 31% (5 of 16) of patients required multiple procedures for removal and that only half attained a satisfactory voice subsequent to Teflon removal. Based on the experience with these patients, our current approach is to attempt total removal.

The results in Table 2 reveal that the use of the CO_2 laser for Teflon removal was not associated with an increased incidence of dysphonia subsequent to Teflon removal. A theoretic concern could be that the increased heat subsequent to laser incisions and dissection would result in greater fibrosis. The data do not support this. Interestingly, the CO_2 laser was not used in patients over 59 years of age — an unexplained finding.

The data presented in Table 1 document that Teflon-related dysphonia occurred in all 4 diagnostic categories. The small numbers prevent any conclusions from these data, but the trend suggests a lower incidence of dysphonia following Teflon removal among patients whose injection was performed for a surgically induced vocal cord paralysis. One could speculate that mobile cords, and immobile cords in the idiopathic group, undergo greater changes in the remaining vocal cord mass subsequent to Teflon removal.

Half (56%) of the patients in this study required a procedure to address the dysphonia that resulted subsequent to Teflon removal. In the majority of cases, a thyroplasty and/or an arytenoid adduction were the procedures used to medialize the vocal cord and improve these patients' dysphonia and other symptoms. In this group of patients, thyroplasty can be a more challenging procedure because of the fibrosis related to the original Teflon injection and the fibrosis related to Teflon removal. It was necessary in some cases to incise sharply the inner perichondrium and underlying scar tissue to allow medialization of the cord. No specific difficulties were associated with arytenoid adduction performed in these patients.

Interestingly, the majority of patients undergoing removal of Teflon were women. The small number of cases in this study does not allow conclusions regarding the importance of this finding. One can speculate that the dimensions of the female larynx predispose to overinjection, or that women are more likely to produce a more exaggerated inflammatory response.

Currently, when patients present with dysphonia and/or airway obstruction secondary to the overinjection of Teflon or an overexuberant inflammatory reaction to Teflon, our approach is to remove Teflon and inflammatory material from the vocal cord via a lateral cordotomy to allow the vocal cord to rest in a midline position with a normal subglottic contour. The medial edge of the vocal cord is left unviolated, in an attempt to preserve a flexible vibratory surface.[10,11] Subsequently, the patient is observed and consideration is given to further attempts to medialize the vocal cord if dysphonia results from a loss of tissue mass or a vocal cord healing in a lateralized position. We have found that the inflammatory reaction associated with the Teflon results in difficulty in judging the final position of the vocal cord, and as well, the subsequent resolution and scarring from further violation of the vocal cord challenge the otorhinolaryngologist to achieve an appropriately medialized vocal cord.

CONCLUSIONS

1. Teflon can be removed from the vocal cords, with resultant improvement in dysphonia.
2. Subsequent to Teflon removal, dysphonia frequently requires a secondary procedure.
3. Thyroplasty and/or arytenoid adduction procedures can be used to successfully manage dysphonia subsequent to Teflon removal.

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OUTCOME OF OPEN SURGICAL THERAPY FOR GLOTTIC CARCINOMA

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A retrospective review was undertaken of the medical records of 270 patients with carcinoma of the glottic larynx. Patients were staged pathologically, and clinical pathologic correlates were made with outcome. In 92 patients with early glottic cancer, the 2-year rate of no evidence of disease for T1 was 98%, and for T2, 84%. Vertical partial laryngectomy resulted in voice preservation in 89%. Patients treated for advanced (T3 or T4) glottic carcinoma underwent total laryngectomy with or without neck dissection. Cervical nodes were involved in 22% of T3 and 41% of T4 patients at the time of treatment. Survival with no evidence of disease was chiefly determined by the development of regional recurrence, distant metastasis, and new primary cancer. Distant metastasis was associated with extracapsular spread ($p = .003$). Patients treated for T4 glottic carcinoma with neck dissection had improved survival compared with patients treated with laryngectomy alone ($p = .006$). Improved survival must be aimed at regional control, prevention, and management of distant metastasis and new primary carcinoma.

KEY WORDS — distant metastasis, glottic carcinoma, laryngectomy, neck dissection, open surgical therapy, outcome, recurrence.

INTRODUCTION

The treatment of patients with laryngeal carcinoma should be planned to provide optimal survival free of disease, with maximum functional results. Based on this concept at the University of Pittsburgh Eye and Ear Hospital, treatment for glottic carcinoma included radiotherapy and endoscopic surgery with or without a laser for superficial cordal lesions. Partial laryngectomy is used for some T1 and T2 lesions. Total laryngectomy alone or in conjunction with various forms of lymph node dissection, and/or postoperative radiotherapy with or without adjuvant chemotherapy, is used for advanced T3 and T4 lesions. The purpose of this report is to review the experience of our institution with open surgery for glottic cancers to assess the effectiveness of treatment and to identify tumor, patient, and treatment factors that may influence local-regional control and distant metastasis and could, therefore, be used to improve our management of glottic carcinoma.

MATERIAL AND METHODS

A retrospective review of the medical records of all patients with squamous cell carcinomas of the glottic region who underwent a definitive open surgical procedure by our faculty between January 1976 and December 1990 was undertaken. Patients who were treated for palliation only or had distant metastasis at the time of their initial evaluation were excluded from this study.

Disease was staged retrospectively by using the criteria set forth in 1992 by the American Joint Committee on Cancer[1] and it was based on clinical descriptions at operations and on pathologic specimen review. Transglottic cancer was defined as glottic cancer with clear evidence of paraglottic extension to the supraglottis. In this study we defined the site of recurrence as local, regional (cervical lymphatics), or distant (metastasis). Only a single site was assigned to each patient. The site nearest to the primary was used. Accordingly, if a patient had local failure and developed distant metastasis subsequently, this patient was put in the local failure group only. Follow-up in our group of patients was at least 2 years. Follow-up information was obtained from the medical records or from personal communication with the patient or the referring physicians. If a patient died of other causes while cancer-free within 24 months of surgery, the case was considered indeterminate. If the patient died cancer-free of other causes after a 2-year period, he or she was considered cured.

All patient charts were reviewed and critical issues were recorded, such as previous irradiation or chemotherapy treatment, the patient's general status, the cervical lymph node status, the presence of extracapsular spread (ECS), and pathologic differentiation of the primary tumor. The impact on survival was

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determined on the basis of these data. The statistical significance of observed events was calculated.

RESULTS

A total of 299 patients treated with an open surgical procedure for various stages of glottic carcinoma were identified, of whom 29 patients either died, free of glottic cancer, of other causes within 2 years, or failed to be followed up in the clinic. These patients are excluded from this study; therefore, 270 patients provide the data for this study. The patients were 28 to 90 years old (mean 63.73 years). There were 238 men and 32 women. Among these 270 people, early cancer (T1 and T2) accounts for 92 patients; T3 and T4 lesions had 144 and 34 cases, respectively.

Among the 92 patients with early glottic cancer, 18 had received previous external irradiation for the primary lesion. All 54 T1 lesions were treated by hemilaryngectomy. Thirty-one of the 38 patients with T2 lesions had hemilaryngectomy, and 7 received total laryngectomy. Among these 7 patients, 4 had previous radiotherapy.

Among the 144 T3 lesions, there were 65 patients with purely glottic lesions and 79 patients with transglottic lesions. In this group, 30 patients had had prior treatment with radiotherapy. Of the pure glottic T3 lesions, 41 (63%) underwent total laryngectomy, while 24 (37%) had total laryngectomy in conjunction with node dissection. Of the transglottic T3 lesions, 34 (43%) patients underwent total laryngectomy, while the other 45 (57%) patients had total laryngectomy with neck dissection. The use of neck dissection was not dependent on primary site ($p > .05$). Thirty patients underwent laryngectomy after failure of full-course radiotherapy. Surgery alone was used as therapy for 92 patients, while 22 patients were treated with surgery plus postoperative radiotherapy.

There were 34 cases of T4 glottic cancer in our study. Eight patients had had prior radiotherapy. Among them, 15 cases were classified as pure glottic lesions. Another 19 cases were transglottic lesions, according to the pathologic report. Fifteen of the 34 (44%) patients underwent total laryngectomy. Nineteen patients (56%) underwent total laryngectomy with neck dissection. In this group of patients with T4 glottic carcinoma, 8 had failed prior full-course radiotherapy. Surgery alone was employed to treat 13 patients, while surgery plus postoperative radiotherapy was administered to 13 patients.

EARLY GLOTTIC CARCINOMA

Neck Metastasis. No patient with a T1 or T2 lesion had neck metastasis at the time of presentation.

Time to Failure. The time to failure in early glottic cancer ranged from 7 to 40 months, with an average of 14.34 months. Eighty-five percent of recurrences were diagnosed within 24 months of surgery.

Local Failure. For T1 lesions, 1 of 54 patients developed glottic recurrence and concurrent lung metastasis. This patient died of disease. Of the 38 patients with T2 neoplasms, 7 developed glottic recurrence. Six of these 7 underwent total laryngectomy with or without neck dissection as the salvage procedure, of whom 4 (67%) had no evidence of disease (NED) after at least 2 years' subsequent follow-up.

Regional Failure. Recurrence in the cervical lymphatics was not observed following treatment of T1 glottic cancer. Cervical recurrence was diagnosed in 4 (10.5%) of 38 patients with T2 lesions, of whom 1 was successfully salvaged with further therapy.

Distant Metastasis. Only 1 T1 case had distant metastasis. This was associated with local recurrence. Distant metastasis as the sole site of recurrence in T1 or T2 carcinoma was not observed.

Two-Year NED Survival. The NED rate for T1 was 98% (53 of 54). The cure rate for patients with T2 lesions was 84% (32 of 38) after salvage of local failure. Among these 92 early cases, there were 81 patients (88%) with voice preservation.

New Primary Cancer. There were 15 (16.3%) new primary lesions in patients with early glottic cancer. Among these, 1 occurred in the contralateral vocal cord. Of these 15 new primaries, 8 directly contributed to the death of the patient.

T3 GLOTTIC CARCINOMA

Neck Metastasis. Cervical metastatic disease was identified at presentation in 19 patients (13%) at the time of diagnosis. Elective neck dissection resulted in the identification of occult metastases in 13 (10.4%) of the 125 patients who had no palpable evidence of metastases. The overall cervical metastatic rate for patients with T3 glottic carcinoma was 22.2% (32 of 144). Extracapsular spread was identified in 12 (37.5%) patients.

Time to Failure. Locoregional recurrent disease was diagnosed within the first 24 months of postoperative follow-up in 83% of patients. In contrast, only 53% of distant metastases were diagnosed within the first 24 months.

Local Failure. Two patients (1.4%) failed in the residual pharynx.

Regional Failure. Ten patients developed metastasis to the jugular chain of lymph nodes, and 7

TABLE 1. IMPACT OF HISTOLOGIC DIFFERENTIATION ON SURVIVAL OF PATIENTS WITH T3 GLOTTIC TUMORS

	Poorly Differentiated (N = 17)		*Well Differentiated (N = 127)*		
	No.	*%*	*No.*	*%*	*p*
Locoregional failure	3	17.65	16	12.60	.5635
Distant metastasis	3	17.65	12	9.45	.2987
No evidence of disease	11	64.71	99	81.10	.1180

patients had stomal recurrence. Treatment of recurrent disease resulted in salvage of 4 patients: 2 with stomal recurrence and 2 with cervical metastasis.

Distant Metastasis. Distant metastasis was the sole site of recurrent disease in 15 patients (10.4%).

Two-Year NED Survival. The 2-year NED survivorship in T3 patients was 79%. The survival figure for patients with glottic primary lesions (80%) was similar to that of patients with transglottic lesions (78%). The presence of prior irradiation, no irradiation, or postoperative irradiation had no apparent impact on ultimate survival (77%, 78%, and 78%, respectively).

New Primary Cancer. A second primary cancer was diagnosed in 22 patients (15.3%) during follow-up.

T4 GLOTTIC CARCINOMA

Neck Metastasis. Six patients of the 34 (17.6%) had demonstrable metastatic disease at the time of preparation. Occult metastatic disease was identified following elective neck dissection in 8 more patients. The overall incidence of neck metastasis was 41% at presentation in patients with T4 glottic carcinoma. Extracapsular spread was demonstrated in 8 (57%) of 14 patients with cervical metastases.

Time to Failure. The average interval between treatment and recurrence in the stoma or cervical region was 8.64 months. In contrast, patients with distant metastasis had an average time to failure of 24 months. All of the regional failures were diagnosed within 2 years, but only 60% of the distant metastases occurred in this time.

Local Failure. No patients failed in the residual pharynx.

Regional Failure. Five patients developed stomal recurrences, while 6 developed cervical metastases. Two of these patients were salvaged (>2 years NED) with subsequent treatment.

Distant Metastases. Distant metastases were the sole site of recurrent disease in 5 of 34 T4 patients (14.7%). This included 4 patients with lung metastases and a fifth patient with metastases to the lung and skin.

TABLE 2. IMPACT OF EXTRACAPSULAR SPREAD ON SURVIVAL OF PATIENTS WITH T3 GLOTTIC TUMORS

	Extracapsular Spread (N = 12)		*No Extracapsular Spread (N = 20)*		
	No.	*%*	*No.*	*%*	*p*
Locoregional failure	4	33.33	3	15.00	.2266
Distant metastasis	4	33.33	1	5.00	.0326
No evidence of disease	4	33.33	16	80.00	.0083

Two-Year NED Survival. Overall, 58% of T4 patients remained NED at 2 or more years after treatment. Patients with purely glottic lesions experienced a lower 2-year NED survivorship (33%) than patients with transglottic lesions (68%). Patients who received prior irradiation demonstrated a 38% (3 of 8) NED survival, compared to 38% (5 of 13) in those treated with surgery alone and 77% (10 of 13) in those treated by surgery plus postoperative irradiation.

New Primary Cancer. The rate of second primary carcinoma diagnosed in patients with T4 laryngeal carcinoma was 17.7%.

A number of factors were evaluated for impact on eventual outcome and disease-free survival. Patients with T3 glottic tumors were analyzed as a single group. Tumor differentiation was not associated with a statistically significant change in either recurrent disease or survival (Table 1). In contrast, ECS was more commonly encountered in patients with T3 transglottic (9 of 21) tumors than in those with T3 glottic (3 of 11) tumors ($p = .018$). Patients with ECS were more likely to have distant metastasis than patients who had cervical metastases without ECS ($p = .033$; Table 2).

The choice of operation was statistically associated with an improved 2-year NED survival rate. Patients treated for T4 glottic carcinoma with total laryngectomy and neck dissection were more likely to remain disease-free than patients treated with total laryngectomy alone ($p = .0064$). This advantage was not observed in patients with T3 primary disease.

DISCUSSION

The laryngeal glottis is defined anteriorly and posteriorly by the anterior and posterior commissures, respectively. The upper boundary of the glottis is a plane passing through the apex of the ventricle, while the lower margin is the imaginary horizontal plane 1 cm below the apex of the ventricle.[1] The most common site for laryngeal carcinoma in the United States is the glottis.[2] In contrast to patients with carcinoma involving the supraglottic larynx, metastatic tumor from carcinoma involving the glottic larynx is relatively unusual until tumors reach an advanced stage. As the tumor expands and crosses the laryngeal ventricle to involve the paraglottic space, an increased potential for cervical metastases exists. Advances in modern imaging contribute enormously in delineating submucosal extension and thereby differentiating glottic lesions from lesions with extended involvement.

Our data indicate that 22% of patients with T3 lesions and 41% of patients with T4 lesions may have identifiable cervical metastases at the time of presentation. The relative risk of developing cervical metastases was similar in disease categorized as glottic and in disease categorized as transglottic. This similarity probably reflects the patient population under study, inasmuch as patients with an extensive supraglottic component to the tumor were not included in this study. The issue of regional recurrence is further emphasized when we analyze the sites of failure in patients with T3 and T4 glottic carcinoma. The primary route of metastasis for lesions that invade the anterior commissure and the subglottic region is to the paratracheal lymph nodes. Among 19 patients with T3 glottic cancer who developed recurrent disease, 10 had metastases to jugular lymph nodes, while 7 others had stomal recurrences. These stomal recurrences should perhaps be regarded as regional metastases. Similarly, among the 11 patients with locoregional failure following treatment for T4 glottic carcinoma, 5 had stomal recurrences and 6 had cervical metastases.

Another factor influencing the long-term survival of patients treated for glottic carcinoma in this series was development of new primary cancer and distant metastatic disease. The overall incidence of developing a second primary carcinoma during the follow-up period was 15.9% overall. The second primary rates for patients with T1, T2, T3, and T4 primary tumors were 7.4%, 29%, 15.3%, and 17.7%, respectively.

No patient with a T1 or T2 glottic primary developed a distant metastatic lesion as the sole site of recurrence. Distant metastasis occurred in 20 patients (11.2%) with advanced laryngeal carcinoma as the sole site of recurrence. All eventually died of disease. The development of distant metastases as the sole site of recurrent disease was related to the presence of ECS in cervical metastases ($p = .033$). As locoregional control of glottic cancer seems to have reached a plateau, further effort must be considered to prevent distant metastasis with systemic therapy in identified high-risk groups of patients.

Last, the overwhelming majority of locoregional recurrences experienced by this group of patients with glottic carcinoma involved either metastasis to the cervical lymphatics following completion of therapy or stomal recurrence. Inasmuch as the primary lymphatic drainage of the glottic larynx is to the paratracheal lymphatics, stomal recurrence should be considered a form of regional metastasis. Accordingly, aggressive management of cervical metastases, especially in patients with advanced glottic carcinoma, must be undertaken. This should include selective neck dissection of zones III and IV, as well as zone VI, including ipsilateral thyroid lobectomy. Patients with histologic evidence of advanced disease including, but not limited to, cervical metastases, cartilage invasion, and subglottic extension greater than 1 cm should be offered postoperative radiotherapy to include the stoma and superior mediastinum.

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VOCAL GRANULOMA, INCLUDING SCLEROSIS OF THE ARYTENOID CARTILAGE: RADIOGRAPHIC FINDINGS

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Vocal granulomas are uncommon benign tumors that may not respond readily to medical treatment or surgical removal. Gastroesophageal reflux is said to be a causative factor. Osteosclerosis of the arytenoid cartilage was found on computed tomographic scan in a series of 21 consecutive patients. The relationship of vocal granuloma to so-called contact ulcer (better called contact pachydermia) is discussed. Imaging of the granuloma and the arytenoid has little, if any, place in management, but should be recognized in the differential diagnosis of a vocal cord mass if the mass lies immediately adjacent to a sclerotic arytenoid.

KEY WORDS — arytenoid osteosclerosis, vocal granuloma.

INTRODUCTION

Vocal granulomas are uncommon but readily recognized, rounded, sometimes bilobed or even multilobed, yellow-pink tumors arising on the posterior third of the vocal cord, near the vocal process of the arytenoid cartilage (Fig 1).[1-3] There may be inflammation of the surrounding mucosa in the posterior glottic space.

Most patients have hoarseness, but the speaking voice may be normal or near normal. There is often a feeling of irritation and a desire to clear the throat. It has been said that patients are aggressive or tense individuals with a loud voice,[4,5] and one useful classification describes vocal granulomas as hyperfunctional, hyperacidic, or intubation types.[6] In many of our patients no such causative factors can be found. Intubation granulomas were excluded from this series.

The diagnosis of vocal granuloma can often be suspected from the clinical features and confirmed by indirect laryngoscopy; visualization of a round, pinkish lesion arising from the arytenoid (Fig 2) strongly suggests the diagnosis. Microlaryngoscopy and excision biopsy for histologic proof excludes malignancy or other specific granuloma.[3]

Gastroesophageal reflux is said to be a cause of vocal granuloma.[4-7] Reflux fluid not only contains acid, but also pepsin, bile acids, and pancreatic enzymes,[7] all of which have the ability to irritate or injure tissues not normally exposed to these substances. Other etiologic factors are considered to be voice overuse, misuse, or abuse; smoking; and alcoholic and dietary indiscretions. Repeated coughing, throat clearing, and irritation in the throat may be factors, but it is possible that these are symptoms secondary to the granuloma itself. Mechanical trauma is described as forceful opposition or "slamming together" of the arytenoids, at the onset of voicing or with excessive throat clearing or chronic cough, causing irritation and injury of the thin mucosa and perichondrium overlying the cartilage.[2,5]

We report an interesting finding shown on computed tomography (CT) of the larynx. The change was first seen in a patient referred by an otologist who had performed CT of the larynx. Not only could the vocal granuloma be seen, but a surprising finding was sclerosis of the arytenoid cartilage on the side of the granuloma. No previous literature reference to radiographic change in patients with vocal granuloma could be found.

MATERIALS AND METHODS

Radiology. With a GE 9800 CT scanner, axial sections were performed (1.5 mm thick with 1.0-mm spacings) through the region of the true and false vocal cords in 21 patients. Images were obtained in quiet respiration to achieve abducted cords. Intravenous contrast was used in only 6 patients, and no reliable value was observed from its use.

The films were read by one of the authors (J.R.), who assessed each case for size, shape, and position of the granuloma. Arytenoid sclerosis was assessed and classified as being mild, moderate, or severe. It was also classified as to its being cortical sclerosis (focal or generalized) or marrow sclerosis. The degree of sclerosis was correlated with the duration of symptoms, number of operative procedures, and size of the granuloma.

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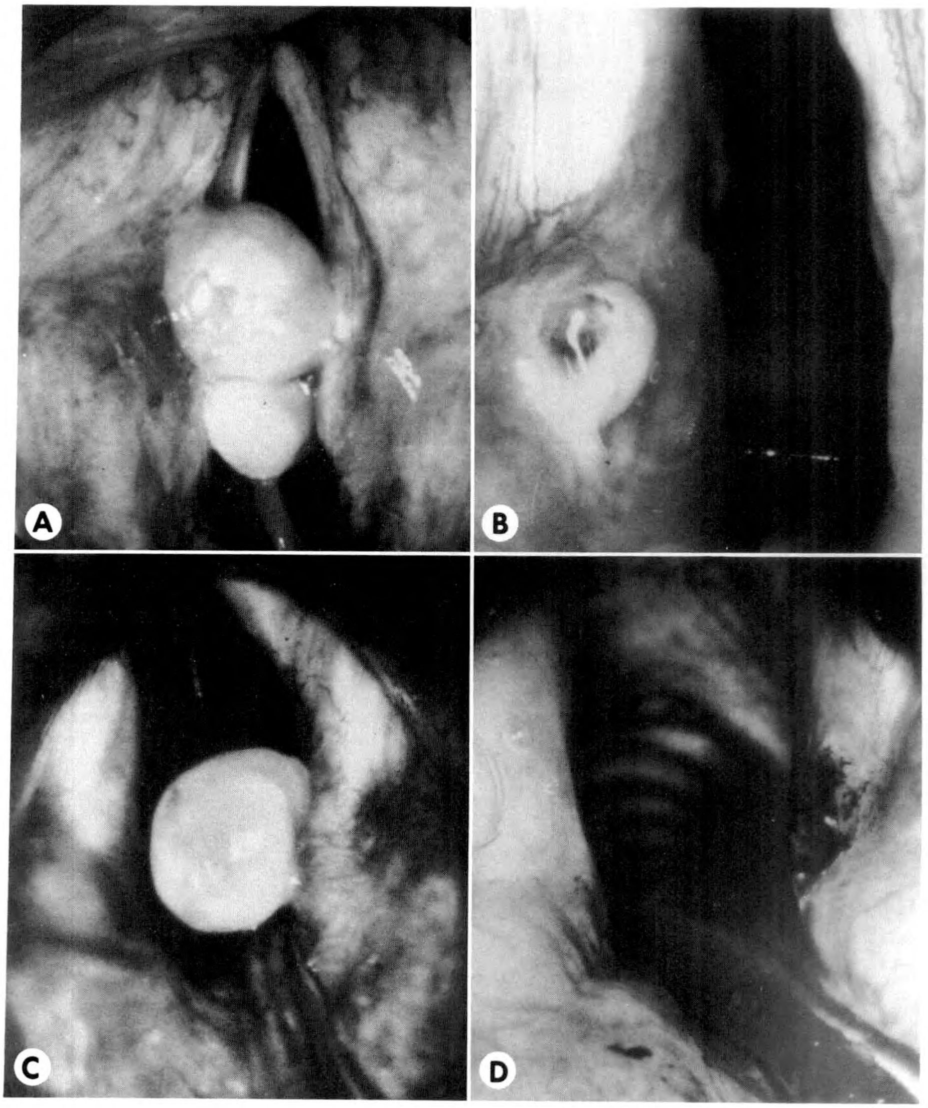

Fig 1. Direct laryngoscopy. A) Large, bilobed granuloma. B) Previously large granuloma that has resolved to small, round remnant. C,D) Granuloma site C) before and D) after removal with carbon dioxide laser.

Assessment of the size of a granuloma is limited, as not all patients were imaged before surgery, and the inferosuperior size of the granuloma was affected by cord movement.

Technique of Removal. Twenty-one consecutive patients with proven vocal granuloma were scanned over an 18-month period. Two had no previous surgery and 19 had already had 1 or more operations for removal of the granuloma, either with forceps and scissors or with a laser.

All 21 patients had microlaryngoscopy and removal with a Zeiss carbon dioxide laser with a beam diameter of approximately 0.8 mm at 4 to 6 W. The granuloma was grasped to expose the pedicle and amputated. We attempted to leave the mucoperichondrium intact, without exposing the arytenoid cartilage, but this was difficult to achieve. In each case the tissue was histologically consistent with vocal granuloma. No specific granulomatous disease or malignancy was found.

RESULTS

All 21 patients were men. The average age was 50 years, with a range from 34 to 79 years. An unexpected finding was that 14 had granulomas on the left and 7 had granulomas on the right side. No patients had bilateral disease. None of the patients had a history of endotracheal intubation.

All patients had some vocal disability; most had a feeling of something in their throat and throat clearing or irritation. Several patients with large granulomas had dyspnea, more marked at night.

Granulomas were clearly seen in 17 of the 21 patients. The 4 patients in whom no granuloma was seen had previous surgical removal and were being investigated for the presence of arytenoid sclerosis.

The site of granulomas was constant: always in the posterior third of the vocal cord and always with a portion of the apparent base of the granuloma related directly to the vocal process of the arytenoid (Fig 3).

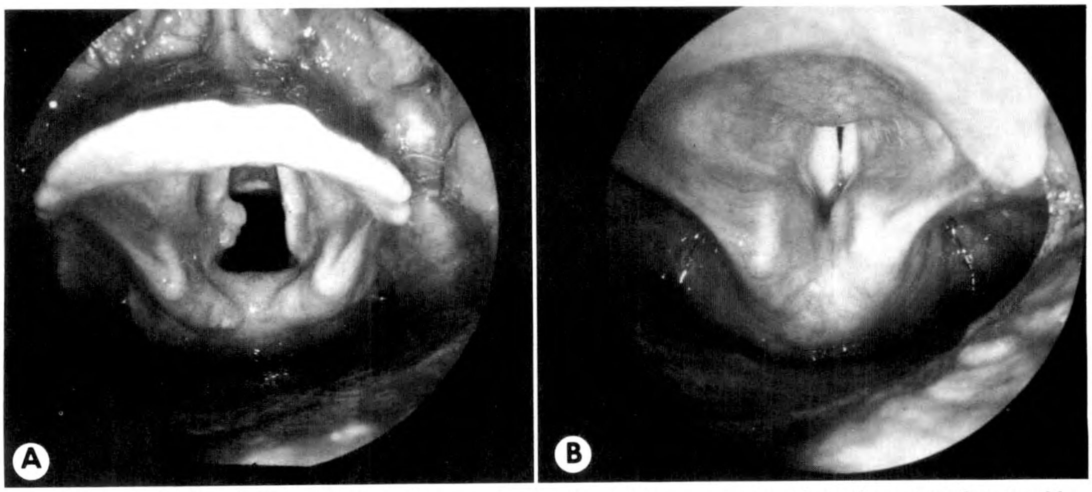

Fig 2. Left vocal granuloma at indirect laryngoscopy. A) Irregular mass region of vocal process of arytenoid during quiet respiration and B) not visible during phonation.

Granuloma size varied from 12 × 14 × 10 mm to 1 × 1 × 2 mm. The larger lesions were seen on slices below the glottis or even to above the false vocal cords. Radiologic assessment of pedunculation was limited, as all lesions appeared sessile, that is, with the base of the lesion as large as or larger than the main granuloma.

Arytenoid sclerosis was constant in all patients. It was more commonly focal than generalized (17 of 21), and when focal, the sclerosis was nearly always medial (16 of 17). Some degree of marrow sclerosis was seen in most patients (19 of 21).

There was no apparent relationship between length of patient symptoms, the size of the granuloma, or the number of operations and the degree of arytenoid sclerosis.

DISCUSSION

Many papers[1,2,4-10] refer to vocal granuloma or contact ulcer — sometimes to ulcer-granuloma as the same disease, without discrimination between ulcer and granuloma. There appears to be no good evidence of a sequence of events or an interrelationship. The so-called ulcerated stage and the granuloma stage may possibly be different stages of the same pathologic process, but it is rare to see the ulcerated stage. Kleinsasser[1] pointed out that in the Anglo-American literature saucer-shaped epithelial thickenings at the tips of the vocal processes are usually called contact "ulcers" and, instead, he uses the term contact pachydermia, because he had not observed the presence of a true ulcer. Vaughan and Strong[11] said that the term contact ulcer should not be used, because the lesion is a crater in the center of a circle of hyperplastic epithelium. Benjamin and Croxson[3] questioned whether ulcer and granuloma are different stages of the same pathologic process, and postulated that each might be regarded as a separate entity. Do granulomas always commence as an ulcer and pass through what might be regarded as the ulcer-granuloma stage with a central crater surrounded by a rim of hypertrophic tissue? There is a lack of convincing proof of the hypothesis that nonspecific granuloma develops on a preexisting ulcer. The former has a pedicle, the latter does not.

Vocal granulomas are often a management problem because of recurrence despite vigorous treatment of gastroesophageal reflux, adequate voice therapy, and surgical removal.

We report additional information about the local pathologic changes as they appear on CT scan. The radiographic change in the arytenoid on the affected side appears to be secondary to the presence of the granuloma and seems to be part of the local pathologic process. It is doubtful if primary disease in the arytenoid leads to formation of the granuloma. Two patients who had not had operative interference had osteosclerotic change, which apparently had occurred prior to surgical trauma. The osteosclerosis in the arytenoid is likely to be secondary to reactive hyperemic and infective changes in the perichondrium at the base of the granuloma, where it originates. One could compare the sclerotic changes in the arytenoid to those seen in the thyroid cartilage and the cricoid cartilage in the presence of chronic inflammation, granulation tissue, or tumors.[12] Knowledge that the changes are chronic and widespread in the arytenoid and are not present in the contralateral arytenoid may give the laryngologist a wider appreciation of the disease process, but as yet does not indicate a change in the current means of treatment.

There is no agreed regimen of management. Bastian

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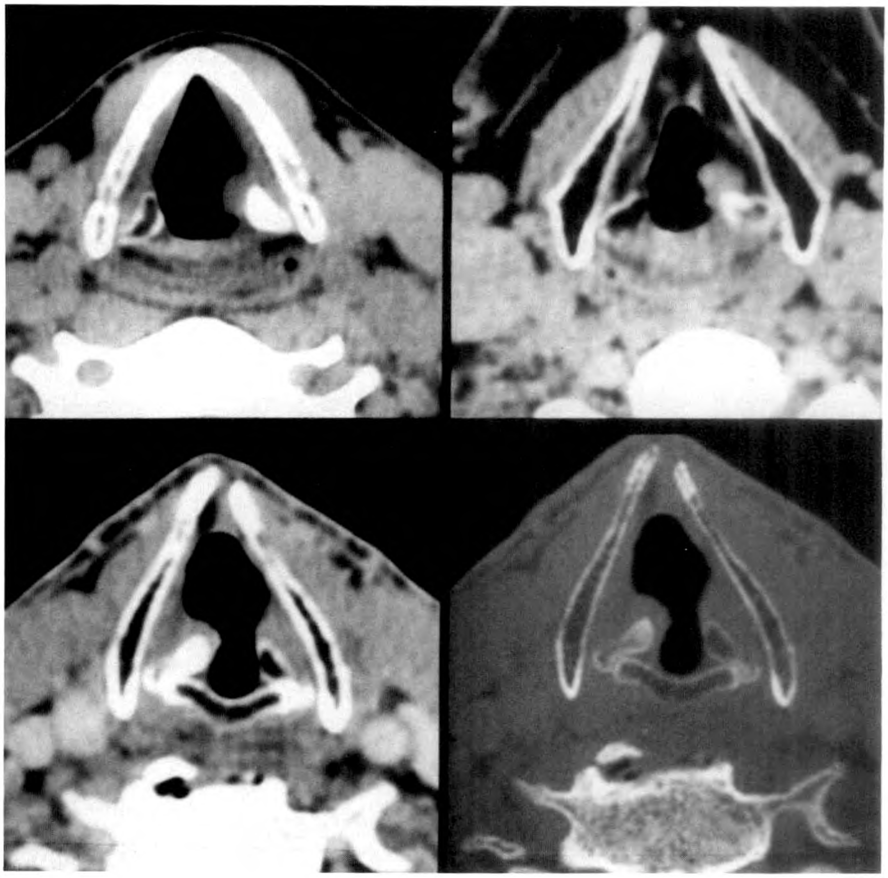

Fig 3. Examples of computed tomograms showing vocal granuloma and associated osteosclerosis of arytenoid cartilage.

states, "Surgery should be a last resort because operative recurrence of the ulcerative granuloma is very common."[7(p1914)] However, it seems reasonable to perform microlaryngoscopy and biopsy removal of a suspected granuloma seen at indirect laryngoscopy to confirm the diagnosis and rule out malignancy; a malignant neoplasm in this site can occasionally resemble a vocal granuloma. Removal can be either with forceps and scissors or, preferably, with laser surgery, which is attended by little or no bleeding, allowing more precise removal with little exposure of cartilage of the vocal process and minimal trauma of the mucoperichondrium. Even with careful surgical removal and strict antireflux measures, the granuloma will sometimes recur or persist for a long time. The indication for further removal will be partial airway obstruction caused by the size of the mass. Small granulomas need not be removed, but should be regularly observed by indirect laryngoscopy.

Some have speculated, on the grounds that trauma to the tip of the arytenoid cartilage is a factor, that removal of the vocal process would eradicate the granuloma,[13] but the results on attempting this were described as disastrous (M. S. Strong, personal communication, 1993).

Because the causative factors have not been proven and there is no universal agreement on therapy or prevention of recurrence, various forms of treatment have been advocated,[4,6,7] including treatment of acid reflux (sometimes given on an empiric basis[6] to patients with no symptoms of reflux), prolonged antibiotic therapy, local injection of steroids, oral steroids, oral zinc sulfate, and repeated removal using scissors, the laser, diathermy, or cryotherapy.[14]

A voice therapist should advise the patient on voice care. Medical management with antacids, histamine antagonists, and dietary advice should be given in appropriate cases, and in selected patients consultation from a gastroenterologist and esophagogastroscopy will be indicated. Explanation and counseling of the patient is important, as is reassurance that the granuloma is not increasing in size or is getting smaller. In our experience all granulomas have eventually healed. It is possible that vocal granuloma is a self-limiting condition whose natural history has never been established.

Vocal granuloma is sometimes a frustrating problem. Neither repeated removal nor medical treatment, including "empiric" treatment of gastroesophageal reflux, is universally beneficial to our patients, and yet, given time, the granuloma always resolves. Could vocal granuloma be a self-limiting condition? When arytenoid sclerosis is complete and the cartilage is calcified, there can no longer be perichondritis or chondritis. Perhaps this change assists our medical and surgical treatment in the resolution of the granuloma.

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FOURTH RESEARCH WORKSHOP ON THE BIOLOGY, PREVENTION, AND TREATMENT OF HEAD AND NECK CANCER

The Fourth Research Workshop on the Biology, Prevention, and Treatment of Head and Neck Cancer, sponsored by the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons, will be held in Arlington, Virginia, on September 8-11, 1994. For further information, contact We Plan Meetings, Inc, Ruth C. Enquist, President, 1503 15th St NE, Rochester, MN 55906; telephone (507) 285-1523; fax (507) 281-8328.

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EFFECT OF TENSION, STIFFNESS, AND AIRFLOW ON LARYNGEAL RESISTANCE IN THE IN VIVO CANINE MODEL

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This study used an in vivo canine model of phonation to determine the effects of airflow on glottal resistance at low, medium, and high levels of recurrent laryngeal nerve (RLN) and superior laryngeal nerve (SLN) stimulation. Static and dynamic trials of changing airflow were used to study the effects of airflow on glottal resistance during phonation. As reported previously, glottal resistance varies inversely as a function of airflow. Increasing levels of RLN stimulation resulted in a statistically significant increase in glottal resistance for each level of airflow evaluated. Variation in SLN stimulation had no statistically significant effects on the relationship between flow and resistance. At airflow rates greater than 590 milliliters per second (mL/s), glottal resistance approached 0.1 mm Hg per mL/s for all levels of RLN and SLN stimulation tested. These data support the collapsible tube model of phonation.

KEY WORDS — airflow, glottal resistance, glottis, larynx, resistance.

INTRODUCTION

Laryngeal airway resistance during phonation is defined as the ratio of subglottal pressure to transglottal airflow. These measures are obtained by using methods described by Smitheran and Hixon,[1] in which oral airflow and oral pressure measures provide estimates of transglottal airflow and subglottal pressure. Glottal resistance was then calculated from these oral measures. Currently, these aerodynamic measures are often included in a clinical phonatory function evaluation because of their diagnostic implications.[2] For example, abnormally low measures of glottal resistance may be associated with glottal incompetence, as found in recurrent laryngeal nerve (RLN) paralysis.[3] On the other hand, high glottal resistance may be associated with spasmodic dysphonia or a hyperfunctional voice disorder.[4]

Direct measures of subglottal pressure and translaryngeal airflow in excised and in vivo canine models of phonation have also been made. Muta and Fukuda[5] studied airflow and pressure relations in excised canine larynges. They found that subglottal pressure increased with increasing airflow, with the rate of increase slowing at high flow levels. Thus, laryngeal resistance decreased as airflow increased in their study. The relationship of subglottal pressure and airflow was first evaluated in an in vivo canine model in 1969 by Koyama et al.[6] An increase in subglottal pressure with increasing airflow was again found. Koyama et al also studied the effect of superior laryngeal nerve (SLN) stimulation on pressure versus flow relationships, by comparing trials with various levels of SLN stimulation for fixed levels of RLN stimulation. They found an increase in glottal resistance between trials with no SLN stimulation and trials with low SLN stimulation. However, no statistical tests were performed to determine the significance of these results.

To further analyze the effects of airflow on laryngeal resistance, Smith et al[7] used an in vivo canine model of phonation to evaluate the effect of increasing airflow on subglottal pressure, while keeping laryngeal nerve stimulation constant. They noted that subglottal pressure increased with increasing levels of airflow during trials in which flow increased dynamically. Contrary to previous findings, Smith et al reported a linear decrease in laryngeal airway resistance with increasing airflow. An explanation of the changes in laryngeal resistance with increasing airflow may be found in the work of Sercarz et al,[8] who used digitized stroboscopic images to measure glottal area per cycle of phonation. Glottal area per cycle of phonation was calculated by integrating the area under the glottal area versus time waveforms created from the measured stroboscopic images.

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Presented at the meeting of the American Laryngological Association, Los Angeles, California, April 17-18, 1993.

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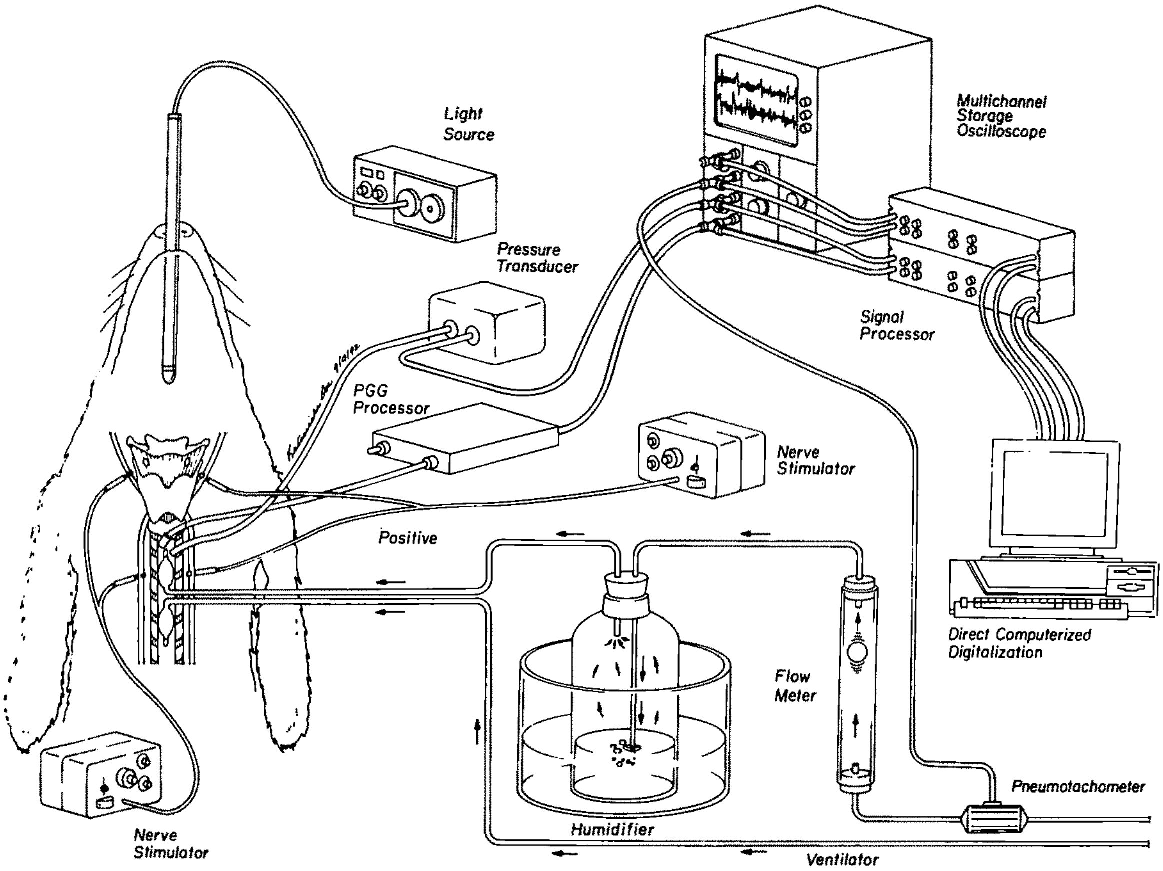

Fig 1. In vivo canine model of phonation.

Multiple trials were made with various levels of airflow. They found that glottal area per cycle increased with increasing levels of airflow, suggesting that the decrease in laryngeal resistance with increasing airflow reported by Smith et al may be due to an increase in glottal area.

Sercarz et al[8] evaluated the effects of airflow on glottal resistance using the formula for rigid wall resistance:

$$R = k\frac{1}{2}\rho\frac{/u/}{A^2}$$

in which k = constant, ρ = density, u = airflow, and A = peak glottic area. In that study, they found an increase in glottal resistance with increasing airflow. This is contrary to the concept of flow through a rigid tube, in which increasing flow is always associated with an increase in rigid tube resistance (due to constant area). These findings are explained by the pliable nature of the glottis and the nonlinear relationship of glottal area to resistance.

However, an understanding of laryngeal resistance involves a knowledge of not only the effects of glottal airflow, but also the effects of different levels of laryngeal nerve activation. No study has evaluated the effects of various levels of both RLN and SLN stimulation on glottal resistance. Previous studies have revealed that an increase in RLN stimulation was associated with a decrease in glottal area per cycle, while an increase in SLN stimulation levels resulted in an increase in glottal area per cycle (Bielamowicz et al, unpublished observations). Also, increasing levels of RLN stimulation resulted in an increased medial adductory compression of the vocal folds.[9] This suggests that measures of glottal resistance should increase with increasing levels of RLN stimulation and decrease with increasing SLN stimulation. This hypothesis was tested in the present study by measuring changes in subglottal pressure and airflow for various levels of SLN and RLN stimulation.

MATERIALS AND METHODS

Animal Model. The in vivo canine model of phonation is depicted in Fig 1 and has been described in detail in previous reports.[10] Two male mongrel dogs, approximately 25 kg each, were selected for this study. Each animal was premedicated with acepromazine maleate intramuscularly. Intravenous thiopental sodium was administered to a level of corneal anesthe-

TABLE 1. SUBGLOTTAL PRESSURE MEASURED FROM OSCILLOSCOPE AT BEGINNING OF EACH DYNAMIC TRIAL FOR EACH COMBINATION OF RLN AND SLN STIMULATION LEVEL DURING EXPERIMENT 1

		RLN Level		
SLN Stimulation Level	*mA*	*Low*	*Medium*	*High*
Low	0.5	25	35	55
Medium	0.8	25	35	55
High	1.2	25	35	55

Data are in centimeters of water.

SLN — superior laryngeal nerve, RLN — recurrent laryngeal nerve.

sia. Additional thiopental sodium was used to maintain this level of anesthesia throughout the procedure.

The animal was placed supine on the operating table. A midline incision was made to expose the trachea from the hyoid bone to the sternal notch. A low tracheostomy was performed at the level of the suprasternal notch and cannulated with an endotracheal tube for ventilation. A second tracheostomy was performed superiorly, and a cuffed endotracheal tube was passed in a rostral direction with the tip positioned 10 cm below the vocal folds. The cuff was inflated and air was passed through this rostral endotracheal tube from a laboratory wall outlet. Airflow was humidified and heated by bubbling through 5 cm of heated water so that the temperature of the air was 37°C when measured at the glottal outlet. Upstream subglottal pressure was measured with a catheter-tipped pressure transducer (Millar Instruments, model SPC-330; Houston, Tex). The subglottal pressure transducer was passed rostrally through the superior tracheotomy and placed 2 cm below the glottis.

Airflow was controlled by a valve at the laboratory wall outlet and measured with a U-tube flowmeter (Gilmont Instruments, model F1500; Great Neck, NY) and a pneumotachometer (Fluid Precision Inc, model 183, Billerica, Mass) prior to airflow humidification. Before recording any trials, the pneumotachometer was calibrated with known levels of airflow from the flowmeter. The Gilmont flowmeter allowed macroscopic control of airflow, while the output of the pneumotachometer was digitized and later analyzed by a personal computer.

One-centimeter segments of the RLN and SLN were isolated bilaterally, and Harvard bipolar electrodes (South Natick, Mass) were applied. A constant current nerve stimulator (WR Medical Electronics Co, model S2LH; St Paul, Minn) was used to stimulate the RLN, and a constant voltage source (Grass Instruments, model 54H; Quincy, Mass) was used to stimulate the SLN. These nerves were stimulated at 70 to 80 Hz, with a current of 0.5 to 2.0 mA (RLN) or 0.5 to 1.2 mA (SLN) for 1.5 milliseconds' pulse duration.

A custom photoglottography (PGG) sensor was placed on the trachea, immediately inferior to the larynx. A xenon light source was secured in the oral cavity to provide transglottal light for excitation of the PGG sensor.

Digitization. A 12-bit analog-to-digital converter housed in a personal computer digitized 3 channels: 1) pneumotachometer signal, 2) PGG waveform, and 3) subglottal pressure signal. Signals were low-pass filtered at 3 kHz and digitized at 20 kHz for 2.8 seconds. The subglottal pressure and PGG signals were verified on a Tektronix oscilloscope (model 5116; Beaverton, Ore) before recording.

Research Design. Two experiments examined the effect of airflow on laryngeal resistance by using the ratio of subglottal pressure to airflow as the formula for resistance. Since glottal area measurements were not obtained in the present study, resistance was not calculated from the formula for rigid wall resistance. While some authors have used PGG as a measure of glottal area, we, as well as other authors, have found this method to be unsatisfactory, because light passing through the translucent vocal folds contributes to the PGG waveform.[11] This makes accurate location of a baseline difficult. Others have pointed out that the light density distribution within the vocal folds does not remain constant throughout a glottal cycle and may adversely affect the PGG signal.[12]

Because each experiment included a large number of phonatory trials, each experiment was performed on a different dog to prevent fatigue effects. In the first experiment airflow varied dynamically. The second experiment used static flow levels. The static trials were used to evaluate the results obtained in the dynamic trials and to alleviate certain difficulties inherent in the dynamic portion of the experimental design, as discussed below.

EXPERIMENT 1

Method. The profile of laryngeal resistance was examined by independently varying airflow, RLN stimulation, and SLN stimulation while measuring subglottal pressure. Values of laryngeal resistance were calculated by dividing subglottal pressure by airflow. Low, medium, and high RLN and SLN stimulation were provided as described in Table 1. Current was set at 0.5, 0.8, and 1.2 mA for low, medium, and high levels of SLN stimulation. Levels of RLN nerve excitation were controlled to produce periodic vocal fold vibration during each trial. The initial RLN stimulation current was determined by monitoring the subglottal pressure oscilloscope trace. For each level of nerve stimulation, the glottal airflow was set initially at 318 milliliters per second (mL/s).

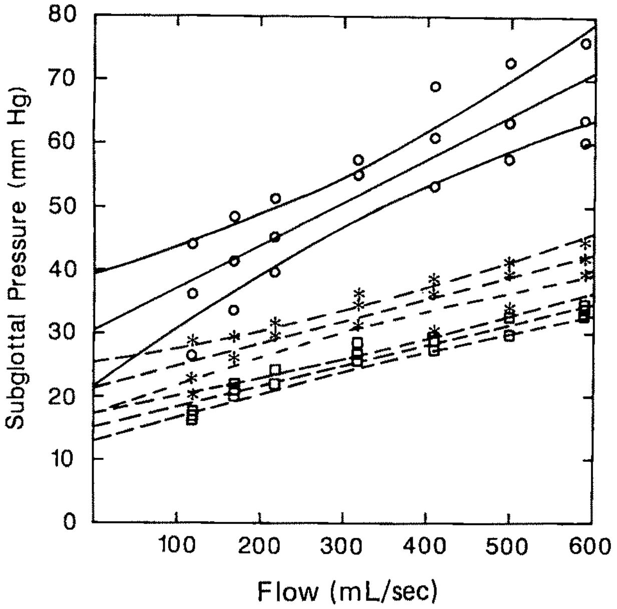

Fig 2. Subglottal pressure versus airflow data for low (squares), medium (asterisks), and high (circles) levels of recurrent laryngeal nerve stimulation. Best fit lines for each level of recurrent laryngeal nerve stimulation are plotted along with curves for 95% confidence intervals.

Current for low levels of RLN stimulation ranged from 0.5 to 0.8 mA as necessary to obtain an initial subglottal pressure of 25 cm H_2O. Medium levels of RLN stimulation varied from 0.8 to 1.5 mA such that the subglottal pressure was 35 cm H_2O at the start of each dynamic trial, while high levels of RLN stimulation produced a subglottal pressure of 55 cm H_2O with 1.5 to 2.0 mA current. After these levels of RLN stimulation were determined for each trial, the RLN level remained constant. The subglottal pressure was allowed to vary freely with changing airflow during each trial. Levels of nerve stimulation were randomized across trials to minimize fatigue effects.

The nerves were stimulated and phonation began. Next, airflow was dynamically increased from 318 mL/s to 590 mL/s by manually increasing flow at the wall outlet over 2.8 seconds, while the stimulation amplitude to the RLN and SLN nerves remained constant. Finally, flow was dynamically decreased from 318 mL/s to 70 mL/s while RLN and SLN stimulation again were held constant. Airflow levels of 70 and 590 mL/s were the end points for the trials because they defined cessation of phonation for this animal. Phonatory trials were obtained for each condition of the experimental design outlined in Table 1. Because of the phonatory fatigue of the dog, multiple trials for all conditions of the experimental design could not be performed.

The subglottal pressure and pneumotachometer signals were analyzed on a personal computer with CSpeech software (Paul Milenkovic, Madison, Wis). First, the pneumotachometer waveform was used to determine airflow levels of 119, 169, 218, 318, 409, 499, and 590 mL/s by converting voltage output into mL/s via the pneumotachometer calibration curve. Once these flow regions within trials were identified, the subglottal pressure tracing was analyzed for each level of airflow by averaging 5 phonatory cycles around the previously measured region of airflow. Peak subglottal pressures were then plotted against flow for each level of RLN and SLN stimulation. Linear regression curves were then used to fit a line to the data points for each condition, and 95% confidence intervals about each line were calculated to determine the significance of differences between the curves. For each combination of subglottal pressure and airflow, resistance was calculated. Resistance values were then plotted against flow for all combinations of RLN and SLN stimulation.

In addition, the fundamental frequency (F_0) was calculated from the PGG waveform by averaging the period lengths of 10 consecutive cycles of stable phonation in a phonatory trial. Three regions of stable phonation were measured for each trial, and the 30 values were averaged. The F_0 was calculated by obtaining the reciprocal of the average cycle duration.

Results. A 1-way analysis of variance showed no significant effect of SLN stimulation level on subglottal pressure ($F_{2,69} = 0.02, p > .05$). Therefore, the data were collapsed across SLN stimulation levels for all subsequent analyses.

Subglottal pressure increased with airflow for the 3 levels of RLN stimulation, as shown in Fig 2. This Figure also includes regression lines with 95% confidence intervals, and reveals a statistically significant increase in the slope of the subglottal pressure versus airflow curves with increasing levels of RLN stimulation. Flow and F_0 were significantly correlated ($r = .65, p < .05$). Therefore, multiple regression was used to predict subglottal pressure from flow levels and F_0 values for each level of RLN stimulation. Significant relationships were found for all levels of RLN stimulation (low stimulation: $F_{2,18} = 228.86, p < .05, R^2 = .96$; medium stimulation: $F_{2,18} = 91.31, p < .05, R^2 = .91$; high stimulation: $F_{2,18} = 34.25, p < .05, R^2 = .79$). For low and medium levels of RLN stimulation, flow and F_0 had independent and significant effects on subglottal pressure (Table 2). For the high level of RLN stimulation, effects were apparently not independent, and neither factor had a significant effect on pressure when the other was controlled for, although the overall regression was significant. Thus, both flow and F_0 affect subglottal pressure for low and moderate levels of RLN stimulation. The effects of

TABLE 2. RESULTS OF MULTIPLE REGRESSION ANALYSIS SHOWING EFFECTS OF FLOW AND F0 ON SUBGLOTTAL PRESSURE AT LOW, MEDIUM, AND HIGH RLN STIMULATION

RLN Stimulation	*Variable*	*Co-efficient*	*Standard Co-efficient*	t	*p* (t)
Low	Constant	9.34	0.00	6.45	<.05
	Flow	0.02	0.49	4.26	<.05
	F0	0.14	0.51	4.49	<.05
Medium	Constant	14.58	0.00	7.98	<.05
	Flow	0.00	0.49	4.23	<.05
	F0	0.14	0.52	4.50	<.05
High	Constant	17.63	0.00	2.39	<.05
	Flow	0.03	0.36	1.26	>.05
	F0	0.19	0.55	1.94	>.05

Both flow and F0 affect subglottal pressure for low and moderate levels of RLN stimulation. Effects of flow and F0 are not separable for high levels of RLN stimulation.

F0 — fundamental frequency, RLN — recurrent laryngeal nerve.

flow and F0 are not separable for high levels of RLN stimulation.

Resistance values decreased as flow increased for each level of RLN stimulation in experiment 1, as shown in Fig 3A. Logarithmic curves provided good fit (r^2) for each level of RLN stimulation. The RLN stimulation condition had a significant effect on resistance ($F_{2,54} = 17.17$, $p < .05$). Scheffé comparisons showed that resistance was significantly greater for the high RLN stimulation condition than for the low or medium stimulation conditions. However, the low and medium RLN stimulation conditions did not differ significantly. As suggested by the findings above, the SLN stimulation level had no significant effect on resistance ($F_{2,54} = 0.21$, $p > .05$), and no RLN level by SLN level interaction was observed ($F_{4,54} = 0.12$, $p > .05$).

EXPERIMENT 2

Method. Because of concerns over the compressibility of nonideal gases and the compliance of the airflow delivery system during the dynamic trials, the results of experiment 1 were confirmed with static airflow trials. The static trials were also designed to eliminate any possible confounding effects of adjusting the RLN stimulation level at the beginning of the dynamic trials in experiment 1 by the oscilloscope trace of the subglottal pressure. A second dog was used in this experiment, for the in vivo model described in experiment 1.

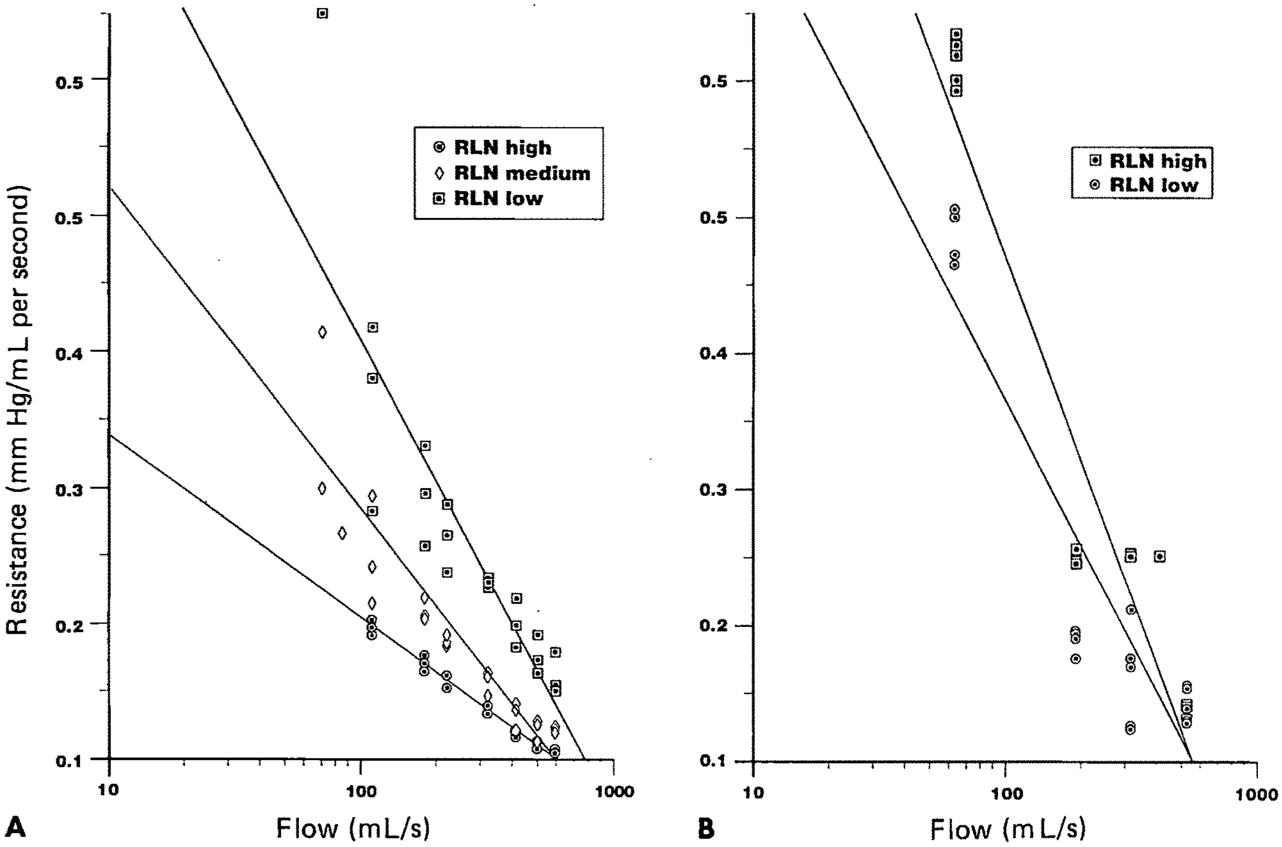

Fig 3. Best fit logarithmic curves for resistance versus airflow. A) For 3 levels of recurrent laryngeal nerve (RLN) stimulation in experiment 1. Correlation coefficients (r^2) for low, medium, and high RLN stimulation are .979, .857, and .786, respectively. B) For 2 levels of RLN stimulation in experiment 2. Correlation coefficients (r^2) for low and high RLN stimulation are .814 and .903, respectively.

A constant level of airflow was confirmed throughout each trial with the Gilmont flowmeter. The RLN and SLN stimulation levels were also held constant within a trial. Current for the low SLN stimulation condition was set at 0.7 mA; current for the high SLN stimulation condition was set at 1.5 mA. The RLN stimulation levels ranged from 0.6 to 0.8 mA for the low stimulation condition, and from 1.3 to 1.5 mA for the high stimulation condition. A narrow range of current was needed to achieve stable phonation in this animal model. The subglottal pressure oscilloscope tracing was not used in this experiment. Flow was set at 63, 183, 318, or 523 mL/s.

Three trials were performed for each experimental condition. However, no trials were performed at a flow level of 318 mL/s when RLN and SLN stimulations were set at high levels because of equipment failure at the end of the experiment. As in experiment 1, the PGG signal was used to determine the F0 for each trial.

Results. A 2-way analysis of covariance examined the effects of RLN and SLN stimulation on subglottal pressure in the second dog while controlling for the effects of F0. As above, increasing RLN stimulation produced significant increases in pressure ($F_{1,46} = 4.44$, $p < .05$). No significant effect of SLN stimulation was observed ($F_{1,46} = 0.58$, $p > .05$), and no interaction occurred ($F_{1,46} = 0.67$, $p > .05$). The F0 did not significantly covary with subglottal pressure in this experiment ($F_{1,46} = 1.32$, $p > .05$), so F0 was not included in subsequent analyses.

Linear regression was used to examine the relationship between pressure and flow for each level of RLN stimulation. Subglottal pressure increased significantly with flow for both RLN stimulation conditions (low stimulation: $F_{1,28} = 52.91$, $p < .05$, $r^2 = .65$; high stimulation: $F_{1,19} = 24.69$, $p < .05$, $r^2 = .57$).

Figure 3B shows that increasing RLN stimulation resulted in an increase in glottal resistance in experiment 2. Logarithmic best fit curves showed a high degree of correlation (r^2) for the resistance versus airflow plots. The RLN stimulation conditions differed significantly ($F_{1,47} = 4.47$, $p < .05$). The SLN stimulation condition did not significantly affect resistance ($F_{1,47} = 0.32$, $p > .05$), and no interaction effect was observed ($F_{1,47} = 0.01$, $p > .05$). These findings confirm the results of experiment 1.

As seen in Fig 3, resistance versus flow curves for the different RLN stimulation conditions converged at approximately 0.1 mm Hg per mL/s as airflow increased. This trend was apparent for both dynamic and static trials. Above this value of glottal resistance, stable phonation ceased regardless of the level of RLN stimulation, SLN stimulation, or airflow.

DISCUSSION

This study examined the effects of airflow, RLN stimulation, and SLN stimulation on laryngeal resistance during phonation by measuring the effect of these variables on subglottal pressure. Dynamic trials provided resistance versus airflow curves of the in vivo canine model of phonation for various RLN and SLN stimulation conditions. Static trials confirmed the effects of airflow, RLN stimulation, and SLN stimulation on laryngeal resistance found in the dynamic trials.

As previously reported, subglottal pressure increased linearly with increasing airflow when RLN and SLN stimulation were held constant.[7] The resistance versus airflow curves (Fig 3) demonstrated a decrease in glottal resistance with increasing airflow in both the dynamic and static trials. These findings are consistent with data from the excised canine laryngeal studies of Muta and Fukuda,[5] who reported a decrease in laryngeal resistance with increasing levels of airflow. The anatomic changes associated with increasing levels of airflow are best explained by the area study of Sercarz et al.[8] They discovered that the glottal area per cycle of phonation increased and glottal resistance decreased with increasing levels of airflow. They speculated that this was due to a greater dilation of the subglottal vault prior to the opening of the glottis with increasing levels of airflow. In addition, Sercarz et al[8] noted that increasing airflow resulted in an increase in F0 due to a shorter closed period during phonation. The authors hypothesized that this finding was due to a decrease in the time required to reach the phonatory threshold pressure, ie, the minimum subglottal pressure required to overcome the glottal closing forces and thus produce glottal opening for each cycle of phonation.

Fundamental frequency increased with increasing airflow in both experiments reported here. This relationship between airflow and F0 is consistent with data reported by Smith et al.[7] They found that the primary determinant of increasing F0 with increasing airflow was due to the effect of increasing subglottal pressure with increasing airflow. In 1989, Titze[13] provided theoretic formulas that predicted the linear effect of increasing subglottal pressure on vibratory frequency of the vocal folds. He stated that the effect of subglottal pressure on F0 resulted from the vocal folds' having "amplitude-dependent frequency" due to the nonlinearity introduced by the dynamic stiffness of the vocal folds. His experimental data from excised canine larynges strongly support the hypothesis that F0 increases with increasing subglottal pressure.

Previous studies have shown that vocal fold thickness decreases and glottal area per phonatory cycle increases with increasing SLN stimulation[14] (also Bielamowicz et al, unpublished observations). On the basis of these data, we anticipated a decrease in glottal resistance with increasing SLN stimulation. However, variations in SLN stimulation had no statistically significant effects on glottal resistance during phonation in the present study. The limited effects of SLN stimulation on glottal resistance are consistent with the findings of Hirano,[14] who reported that SLN stimulation levels had no significant effects on glottal area. The present study contradicts the in vivo canine study of Koyama et al,[6] who found that increasing levels of SLN stimulation tended to increase glottal resistance. However, their conclusions were not supported by statistical analysis.

The effects of various levels of RLN stimulation on glottal resistance have not been studied previously. Increasing levels of RLN stimulation caused a statistically significant increase in the glottal resistance. A previous study has shown that glottal area per cycle of phonation decreased with increasing levels of RLN stimulation (Bielamowicz et al, unpublished observations). We hypothesize that this narrowing of the glottal opening caused an increase in glottal resistance during phonation.

The present results support the collapsible tube model of phonation described by Berke et al[15] in 1991. While the collapsible tube model of vocal fold vibration has not been universally accepted, we believe it provides a useful framework for understanding our results. This model uses measures of external pressure (eg, laryngeal muscle medial adductory forces), downstream pressure drop (eg, transglottal pressure gradient), and elasticity (eg, vocal fold stiffness) to explain why oscillation occurs at moderate flow rates but not at very low or high rates of flow. Berke et al found that spontaneous oscillations begin in the larynx with increasing airflow after the closing forces of the fixed glottal resistor are overcome. During this range of airflow, the glottis is seen as a partially collapsed tube. As airflow increases, the glottis dilates and the pressure drop across the glottis (ie, laryngeal resistance) decreases. Given constant muscular contraction and tissue elasticity, vibration ensues. The collapsible tube model of phonation predicts that increases in airflow will result in an increased vibratory frequency and a decreased glottal resistance (eg, pressure drop), as reported here. This suggests that at low flow rates a higher resistance system exists when the glottis is narrowed, while high flow results in a distended glottis and a lower resistance to airflow. The tube also continues to dilate with increased flow, approaching a circular configuration at very high flow rates.

The collapsible tube model of phonation further predicts that increasing stimulation to the RLN (ie, increasing external pressure on the tube) will produce an increase in glottal resistance at low flow rates, but at high flow rates glottal resistance measures would converge toward the same value despite the extent of laryngeal muscular contraction. Consistent with this theory, all resistance versus airflow curves from this study approached 0.1 mm Hg per mL/s at the highest levels of airflow. Levels of airflow greater than 590 mL/s resulted in the cessation of phonation as the glottis obtained a circular configuration. Therefore, a resistance of 0.1 mm Hg per mL/s defines the minimum level of glottal resistance required for stable phonation, regardless of the level of SLN or RLN stimulation.

CONCLUSION

This study evaluated pressure-flow relationships during phonation in the in vivo canine model of phonation. We found that an increase in airflow resulted in an increase in subglottal pressure, a decrease in laryngeal resistance, and an increase in F0. Increasing levels of SLN stimulation were not found to have a statistically significant effect on laryngeal resistance. However, increasing RLN stimulation caused a significant increase in the glottal resistance for each level of flow tested. In addition, despite the RLN stimulation used, measures of glottal resistance with increasing airflow converge toward the same value. These findings are consistent with the collapsible tube model of phonation.

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FUNCTION OF THE THYROARYTENOID MUSCLE IN A CANINE LARYNGEAL MODEL

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Fundamental frequency is controlled by contraction of the thyroarytenoid (TA) and cricothyroid (CT) muscles. While activity of the CT muscle is known to tense and thin the vocal folds, little is known about the effect of the TA muscle on vocal fold vibration. An in vivo canine laryngeal model was used to examine the role of the TA muscle in controlling phonation. Isolated TA muscle activation was obtained by stimulating sectioned terminal TA branches through small thyroid cartilage windows. Subglottic pressure measures, electroglottographic and photoglottographic signals, and acoustic signals were obtained in 5 mongrel dogs during dynamic and static variations in TA muscle activity. Results indicated that TA muscle activation is a major determinant in sudden shifts from high-frequency to modal phonation. Subglottic pressure increased and open quotient decreased gradually with increasing TA activation.

KEY WORDS — fundamental frequency, in vivo canine laryngeal model, phonation, recurrent laryngeal nerve, thyroarytenoid muscle.

INTRODUCTION

Vocal control during speech or singing is achieved by coordination of the respiratory, laryngeal, and articulatory muscles. Among laryngeal muscles, the cricothyroid (CT) and thyroarytenoid (TA) have been considered tensors of the vocal folds. Arnold[1] claimed that the TA and the CT muscles are in an agonist-antagonist relationship, one being an internal tensor and the other an external tensor of the folds.

The CT muscle is stimulated by an external branch of the superior laryngeal nerve (SLN), and CT muscle activation lengthens and thins the vocal folds. Many studies have clarified the function of the CT muscle in phonation, using electromyography (EMG),[2-4] morphological techniques,[5] and in vivo canine experiments.[6] According to the body-cover theory,[7,8] tension in the cover (the epithelium and the superficial and intermediate layers of the lamina propria) is the primary determinant of fundamental frequency (F0). Contraction of the CT muscle increases the length of the vocal folds, thus increasing the stiffness of the cover to produce an increase in F0.

The role of the TA muscle in F0 regulation is less clear. Hirano et al[3] showed that EMG activity in the TA increased with increasing F0. However, EMG levels dropped when the vocal register shifted to falsetto. Faaborg-Andersen[2] also found increases in EMG activity with increased F0, but across register boundaries EMG activity increased less than for a similar pitch range without a register shift. In contrast, Gay et al[4] reported no drop in EMG activity as F0 increased through 90% of a subject's pitch range. Finally, Larson and Kempster,[9] Kempster et al,[10] and Titze et al[11] found both increases and decreases in F0 after direct electrical TA muscle stimulation during phonation. Apparently, F0 correlates positively with TA muscle activity at lower F0s and lower vocal intensities, but at higher F0s and lower intensities, an increase in TA activity tends to lower the F0.

The present study used an in vivo canine laryngeal model[12,13] to examine the effect of TA muscle stimulation on F0, subglottic pressure, vocal intensity, and open quotient (OQ) during phonation. Isolated TA muscle activation was obtained by stimulating sectioned terminal TA branches of both recurrent laryngeal nerves (RLNs) through small thyroid cartilage windows. This technique enabled us to manipulate levels of TA and SLN stimulation independently, and thus to separate their effects on phonation.

METHODS

In Vivo Preparation. Five mongrel dogs were premedicated with an intramuscular injection of 3 mL acepromazine maleate, followed by intravenous pentobarbital sodium (Nembutal) titrated to loss of

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From the Laryngeal Physiology Laboratory, Division of Head and Neck Surgery, University of California–Los Angeles School of Medicine, Los Angeles, California. This research was supported by a National Institutes of Health grant (R01 DC00855-01) and by Veterans Administration research funds. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of UCLA School of Medicine.

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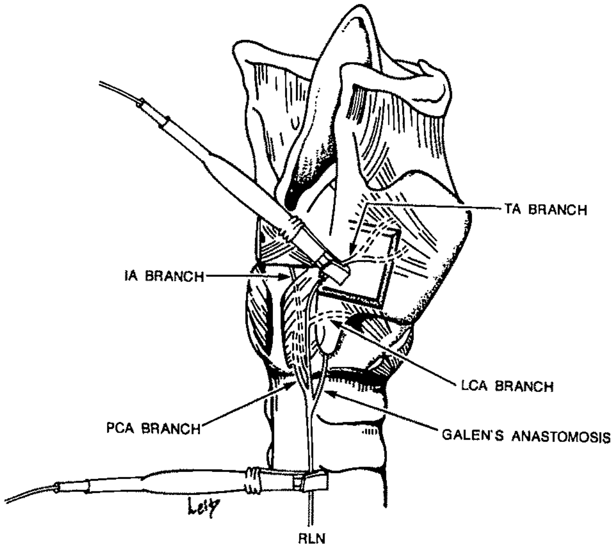

Fig 1. In vivo canine model. Cartilage windows were made at lateral margin of thyroid cartilage to expose thyroarytenoid (TA) branch of recurrent laryngeal nerve (RLN). This branch was cut distal to lateral cricoarytenoid (LCA) branch, and electrode was applied. IA — interarytenoid, PCA — posterior cricoarytenoid.

corneal reflex. Each animal was placed supine on an operating table and direct laryngoscopy was performed to confirm normal laryngeal anatomy. A 7-mm oral endotracheal tube was inserted and connected to a respirator. The animal was shaved, prepared, and draped, and a vertical midline incision was made. The strap muscles and sternocleidomastoid muscles were retracted laterally to expose the larynx and trachea.

The external branch of the SLN was isolated at its entrance into the CT muscle. The RLN was isolated at the tracheoesophageal groove, and its identity was confirmed with electrical stimulation. The inferior constrictor muscle was cut at the lateral margin of the thyroid cartilage. A cartilage window was made with heavy scissors at the lateral-inferior border of the thyroid cartilage. By means of meticulous dissection, the terminal branches of the RLN were located without injuring the intrinsic laryngeal muscles. After stimulation confirmed the lateral cricoarytenoid (LCA) and TA branches, the TA branch was cut 2 mm distal to the LCA branching.

Specially designed rubber electrodes (monopolar, flexible, conductive neoprene with silicone, coated by insulative silicone KE45W) were applied bilaterally as shown in Fig 1. The first was applied around the sectioned terminal TA branch. The second was applied to the main trunk of the RLN to stimulate the other adductor branches (eg, LCA and interarytenoid branches). A third electrode was applied to the external branch of the SLN.

Electrodes attached to each SLN were connected to a Grass model 54H stimulator (Grass Instruments, Quincy, Mass). Electrodes attached to the sectioned TA branches and to the RLN trunks were connected to separate channels of a second nerve stimulator (custom-made, 2-channel, constant-voltage DC stimulator). A ground electrode was inserted into the subcutaneous tissue of the neck flap. Nerves were stimulated with 80-Hz pulses with a 1.5-millisecond duration. Intensity varied from 0 to 3 V, as described below.

A low tracheotomy allowed replacement of the endotracheal tube connected to the respirator, and the oral intubating tube was removed. The epiglottis was suspended with a small button and a 2-0 silk suture for better visualization of the larynx. An additional higher tracheotomy was performed through which a cuffed tracheotomy tube was placed with its tip resting 10 cm below the glottis. The cuff of the superiorly directed tube was inflated to just seal the trachea. Room air was bubbled through 5 cm H2O at 37°C for warming and humidification and passed through the cephalad tracheotomy tube.

Glottography, Pressure, and Intensity Measurements. Electroglottography (EGG) electrodes (Synchrovoice, Briarcliff Manor, NY) were placed in direct contact on either side of the thyroid cartilage. The reference electrode was sutured to the inside of the skin flap.

A photosensor (Centronics OSD 50-2, Mountainside, NJ) was placed on the animal's trachea, approximately 3 cm below the larynx. A halogen flashlight provided supraglottic illumination for photoglottography (PGG).

A catheter-tipped pressure transducer (Millar Instruments, model SPC 330, Houston, Tex) was inserted through the upper tracheotomy and rested 2 cm below the glottis. The transducer was calibrated against a manometer from 0 to 100 mm Hg just before insertion. Intensity was measured with a linear-scale sound level meter (Quest Electronics, model 208L, Oconomowoc, Wis) positioned 30 cm from the larynx.

The PGG, EGG, subglottic pressure, and acoustic signals were low-pass-filtered at 3 kHz and digitized at 20 kHz with a 12-bit analog-to-digital converter installed in a personal computer. The signals were verified on an oscilloscope (Tektronix 5116, Beaverton, Ore) prior to recording. A multipurpose computer program (CSpeech 3.1) was used to analyze the subglottic pressure, glottography (EGG and PGG), and acoustic signals (Fig 2).

Videostroboscopy. Stroboscopic images of vocal fold movement during phonation were recorded with

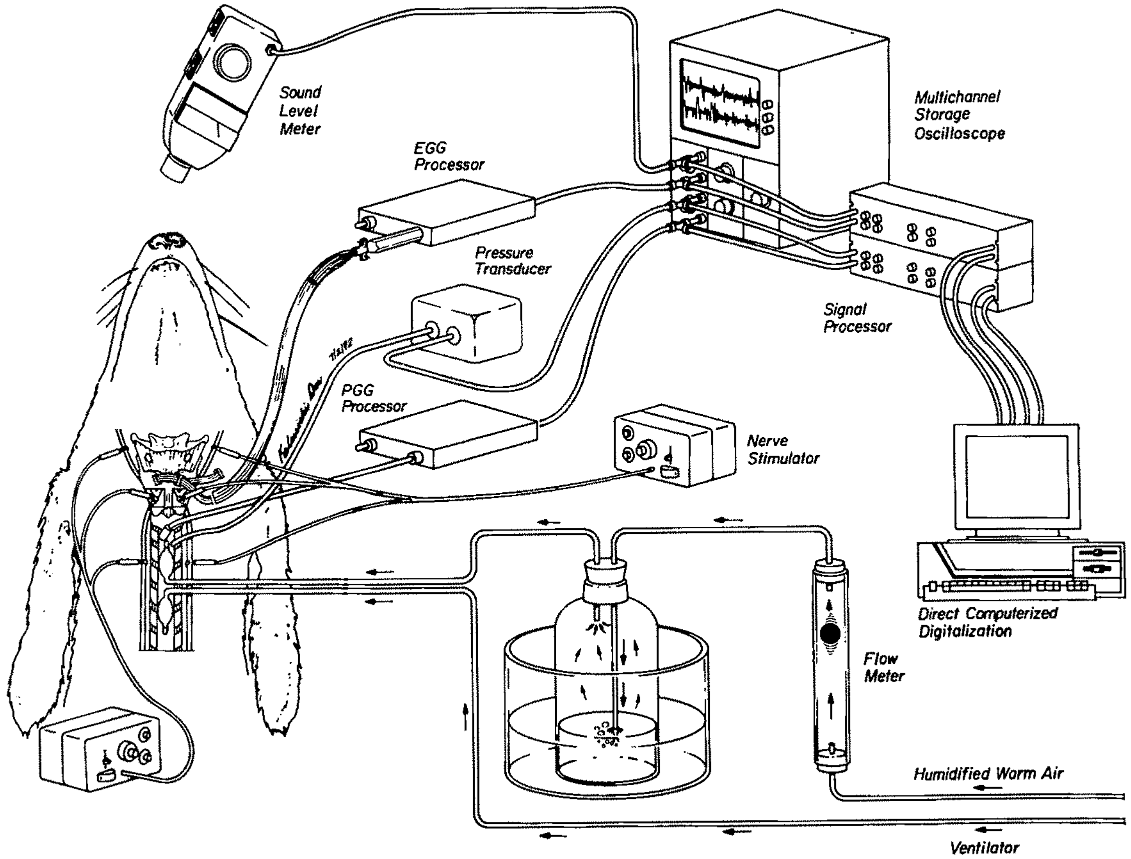

Fig 2. Schematic drawing of experimental model. EGG — electroglottographic, PGG — photoglottographic.

a Storz laryngostroboscope (model 8000). A Storz 0° telescope was connected to the stroboscope via fluid-filled cables. The image from the telescope was recorded with a Storz CCD (charge-coupled device) video camera (model 9000) and a Sony U-Matic videocassette recorder (VO-5800).

Experimental Design of Dynamic Study. Airflow remained constant at 388 mL/s during the experiment. Phonation was induced by stimulating the trunk of the RLN. The level of stimulation was set between 1.5 and 2.0 V as necessary to initiate phonation. Stimulation to the TA branch was then varied gradually from 0 to 3 V over a 3-second trial, during which EGG, PGG, and acoustic signals were digitized. Finally, a second trial was performed by the same procedure in the presence of SLN stimulation at a constant intensity of 3 V.

Data were evaluated at 300-millisecond intervals. Values of F0, subglottic pressure, and OQ were averaged across 10 consecutive cycles for each interval.

Experimental Design of Static Study. Airflow was held constant at 388 mL/s, and RLN stimulation was adjusted as described above. Three levels of stimulation to the TA branch of the RLN were used: zero (0 V), low (1.5 V), and high (3 V). Three levels of SLN stimulation were also used (0 V, 1.5 V, and 3 V).

Each trial lasted 0.5 second, and 2 or 3 trials were obtained for each level of TA branch stimulation. Trials were separated by at least 3 to 5 minutes to reduce fatigue effects. Subglottic pressure, F0, and OQ were measured from 10 consecutive cycles selected at random from a stable section of phonation.

RESULTS

Videostroboscopic Findings. Figure 3 shows the laryngeal configurations produced by the different stimulation conditions. The resting state is shown in Fig 3A. Stimulation of the sectioned TA branch (Fig 3B) produced unique medial bulging of the membranous vocal fold, as reported by Hirano.[7] Some vocal fold adduction was also noted. However, the posterior commissure and the vocal processes were separated widely. Conversely, with stimulation of the RLN trunk (which contains all the adductor fibers except the TA branch), the vocal processes and the posterior commissure were adducted completely, but a chink remained in the middle of the membranous vocal fold (Fig 3C). Combined stimulation of the TA branch and the trunk of the RLN produced total adduction of the vocal fold (Fig 3D).

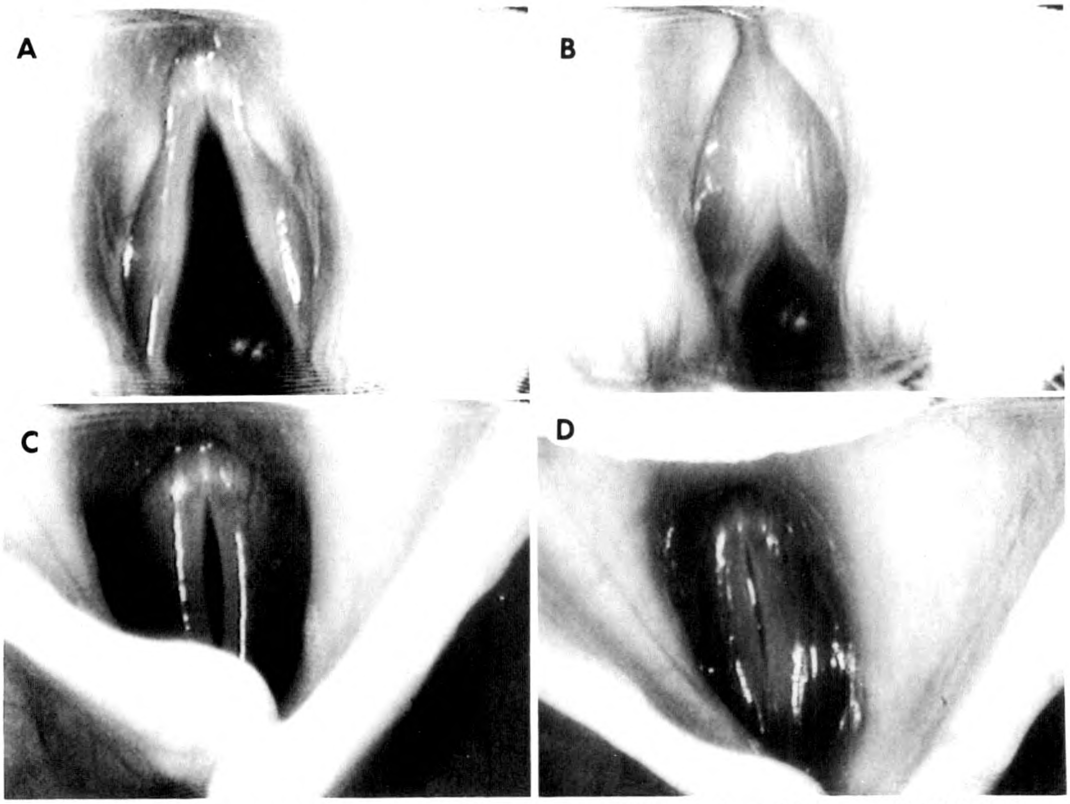

Fig 3. Photographs taken from videotape. A) Resting state. B) Stimulation of TA branch. Medial bulging of membranous vocal fold with some adduction was noted. C) Stimulation of RLN trunk without TA branch. Chink is seen in midmembranous vocal fold. D) Stimulation of RLN together with TA branch. Vocal fold is completely closed.

Dynamic Study. A 2-way (dog by SLN stimulation condition) multivariate analysis of variance (MANOVA) for dependent variables F0, pressure, and OQ showed significant differences among dogs in levels of F0 ($F_{4,80} = 6.55$, $p < .05$) and OQ ($F_{4,80} = 8.81$, $p < .05$). However, no significant interactions occurred between dog and SLN level for any dependent measure (F0: $F_{4,80} = 1.60$, $p > .05$; pressure: $F_{4,80} = 1.45$, $p > .05$; OQ: $F_{4,80} = 1.00$, $p > .05$). Because differences among dogs did not interact with SLN condition, all 5 dogs were combined in the analyses described below.

Some of the dependent measures were moderately but significantly correlated (pressure and OQ: $r = -.69$, $p < .05$; F0 and OQ: $r = .49$, $p < .05$). Accordingly, multiple regression was used to examine the relationship between TA stimulation and these measures. Separate analyses were undertaken for the SLN-on and SLN-off conditions. When SLN stimulation was absent, changes in TA stimulation produced significant changes in pressure and in OQ ($F_{3,41} = 23.51$, $p < .05$, $r^2 = .63$; pressure: $t = 3.65$, $p < .05$; OQ: $t = -2.04$, $p < .05$; Fig 4A,B). The F0 did not vary significantly with TA stimulation ($t = -0.79$, $p > .05$). In the presence of SLN stimulation, only pressure varied significantly with TA stimulation ($F_{3,41} = 53.49$, $p < .05$, $r^2 = .80$; pressure: $t = 6.93$, $p < .05$; Fig 4C). No significant changes in OQ or in F0 were observed (OQ: $t = -0.80$, $p > .05$; F0: $t = -1.11$, $p > .05$).

Although no overall significant effect of TA stimulation on F0 was observed, Fig 5A suggests that when SLN stimulation was present all 5 animals experienced sudden shifts in phonatory frequency as TA stimulation increased. The F0 did change significantly at this point for all dogs ($F_{1,35} = 485.47$, $p < .05$). Further, for every dog subglottic pressure began to rise at the point at which the frequency shifts occurred. However, simple regression confirmed that TA stimulation had no other significant effect on F0, either before ($F_{1,16} = 3.26$, $p > .05$) or after ($F_{1,30} = 0.70$, $p > .05$) the frequency shift. A frequency shift occurred for only 1 dog when SLN stimulation was absent (Fig 5B).

Static Study. Means for the dependent variables for each level of TA and SLN stimulation are given in Table 1. A 2-way (TA stimulation level by SLN stimulation level) MANOVA showed significant effects of TA stimulation on all the dependent measures (F0, pressure, intensity, and OQ). The effect of SLN stimulation level was significant only for intensity

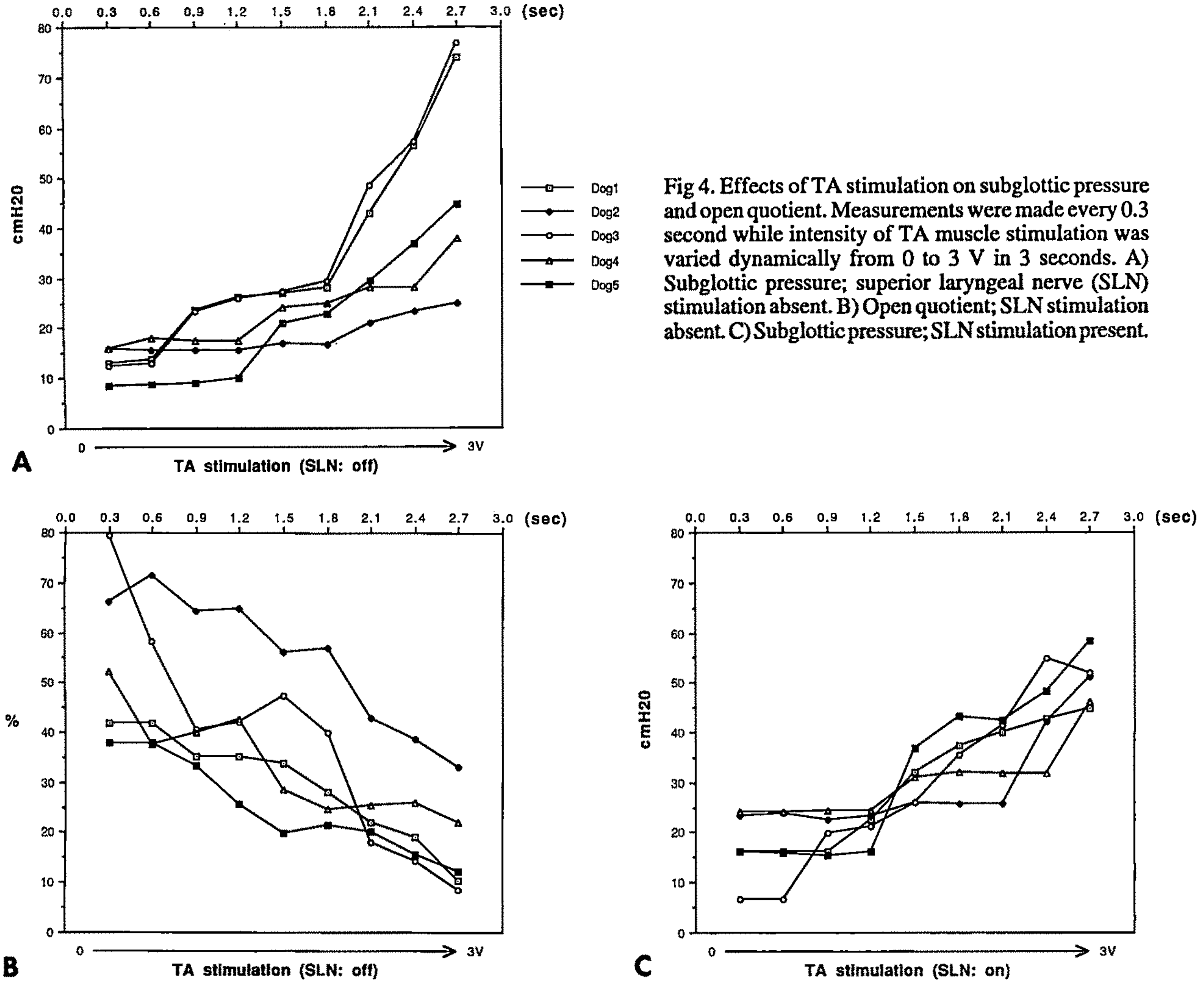

Fig 4. Effects of TA stimulation on subglottic pressure and open quotient. Measurements were made every 0.3 second while intensity of TA muscle stimulation was varied dynamically from 0 to 3 V in 3 seconds. A) Subglottic pressure; superior laryngeal nerve (SLN) stimulation absent. B) Open quotient; SLN stimulation absent. C) Subglottic pressure; SLN stimulation present.

(Table 2). Because the dependent variables were significantly correlated, step-down analysis was used to determine which effects of TA stimulation represented independent effects of stimulation, and which were merely artifacts of these correlations.

In the step-down analysis, the MANOVA described above was repeated with pressure treated as a

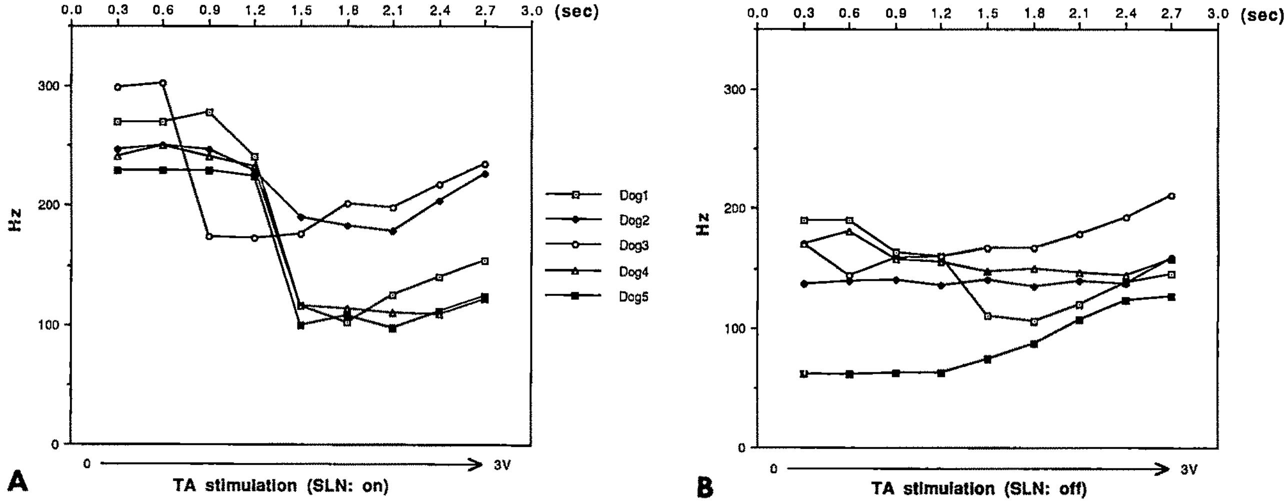

Fig 5. Effect of TA stimulation on fundamental frequency, which was measured every 0.3 second while intensity of TA muscle stimulation was varied dynamically from 0 to 3 V in 3 seconds. A) SLN stimulation present. B) SLN stimulation absent.

TABLE 1. MEANS AND STANDARD DEVIATIONS FOR DEPENDENT MEASURES UNDER VARIOUS LEVELS OF TA AND SLN STIMULATION (STATIC TRIALS)

Independent Variables		*Dependent Variables*			
TA Stimulation	*SLN Stimulation*	*F0*	*Subglottic Pressure*	*Open Quotient*	*Intensity*
Absent	Absent	155.48 ± 42.21	19.94 ± 8.03	60.92 ± 15.63	79.90 ± 5.19
Absent	Low	166.00 ± 16.35	20.82 ± 8.74	47.02 ± 4.99	90.00 ± 10.15
Absent	High	208.26 ± 24.90	19.66 ± 6.65	52.85 ± 10.99	90.40 ± 6.88
Low	Absent	132.52 ± 36.32	38.04 ± 8.21	33.26 ± 4.36	89.20 ± 3.22
Low	Low	120.49 ± 32.31	27.02 ± 3.19	32.56 ± 12.23	87.00 ± 2.00
Low	High	161.18 ± 41.40	34.40 ± 11.14	35.78 ± 6.16	95.50 ± 3.37
High	Absent	204.84 ± 61.11	57.96 ± 20.42	27.38 ± 7.38	96.20 ± 3.19
High	Low	191.76 ± 74.34	54.74 ± 23.47	24.70 ± 10.48	96.80 ± 2.10
High	High	186.00 ± 50.48	49.46 ± 9.52	25.06 ± 3.67	97.80 ± 0.86

TA — thyroarytenoid, SLN — superior laryngeal nerve, F0 — fundamental frequency.

covariate and F0, intensity, and OQ as dependent variables. The effects of TA stimulation on F0 and OQ were still significant after controlling for the correlation between these variables and pressure (F0: $F_{2,80} = 50.98$, $p < .05$; OQ: $F_{2,80} = 55.84$, $p < .05$), but no significant effect on intensity was observed ($F_{2,80} = 2.30$, $p > .05$). Next, F0 was added as a covariate, and the MANOVA was again repeated with dependent variables intensity and OQ. The effect of TA stimulation on OQ remained significant after controlling for correlations with F0 and pressure ($F_{2,79} = 17.77$, $p < .05$).

As in the dynamic trials, sudden shifts in F0 occurred as TA stimulation increased (Fig 6). (Recall that there was no overall effect of SLN stimulation on F0.) Post hoc Scheffé comparisons showed that the F0s obtained in the low-TA stimulation condition differed significantly from those in the TA stimulation-absent and high-TA stimulation conditions ($p < .01$), but that the TA stimulation-absent and high-TA stimulation conditions did not differ significantly from one another ($p > .01$).

DISCUSSION

To summarize our findings, TA stimulation had a significant effect on pressure in dynamic trials, regardless of SLN stimulation level. The effect on OQ was also significant, but only in the absence of SLN stimulation. Across SLN stimulation levels in static trials, TA stimulation had significant and independent effects on pressure, F0, and OQ. The effect on intensity was apparently an artifact of the intercorrelation among dependent measures. Across TA stimulation levels, SLN stimulation had a significant effect only on intensity. Sudden shifts in F0 occurred as TA stimulation increased in both the static and dynamic trials.

TABLE 2. SIGNIFICANCE TESTS FOR STATIC TRIALS

Independent Variables	*Dependent Variables*	df	*F*	*p*
Thyroarytenoid stimulation level	Fundamental frequency	2, 81	11.99	<.05
	Pressure	2, 81	54.69	<.05
	Intensity	2, 81	32.60	<.05
	Open quotient	2, 81	71.66	<.05
Superior laryngeal nerve stimulation level	Fundamental frequency	2, 81	2.72	>.05
	Pressure	2, 81	1.15	>.05
	Intensity	2, 81	11.64	<.05
	Open quotient	2, 81	2.90	>.05

Laryngeal EMG studies of human[3,4] and canine[12-14] phonation have helped establish which muscles control F0, intensity, and frequency (register) shifts during vocalization. However, such studies are not ideal for clarifying the functions of individual muscles or for distinguishing the effects of laryngeal muscles from the contributions of the respiratory system. Despite differences in structure between human and canine larynges,[5] in vivo canine studies are well suited for examining these questions,[15] because the basic gross function of the major laryngeal muscles is quantitatively the same for the 2 species.[16]

Most authors distinguish 3 vocal registers: falsetto or light, modal or heavy, and vocal fry.[17] Falsetto is traditionally characterized by the absence of complete glottal closure, high F0, and low intensity. Modal register is accompanied by complete glottal closure for each vibratory cycle. Vocal fry is characterized by an extremely long closed phase relative to the length of a vibratory cycle. In this study, when phonation was evoked by stimulating the RLN trunk without the TA branch, a weak, falsettolike voice was produced. Regardless of the level of SLN stimulation, the subglottic pressure was lower (below 25 cm H_2O), and OQ was higher than when TA stimulation was present. We could easily hear the sudden drop in F0 and an associated change in voice quality.

When SLN stimulation was present, the drop in F0

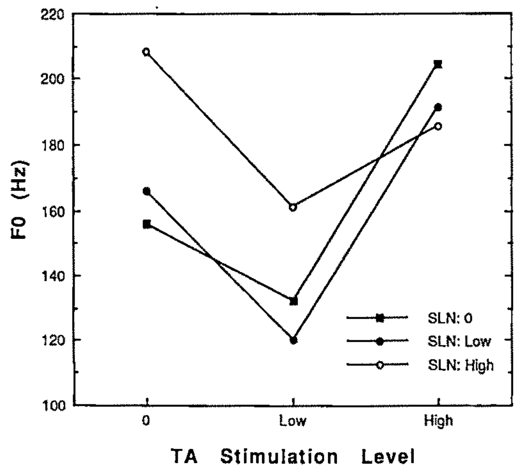

Fig 6. Effect of TA stimulation on F0 in static trials, with and without SLN stimulation.

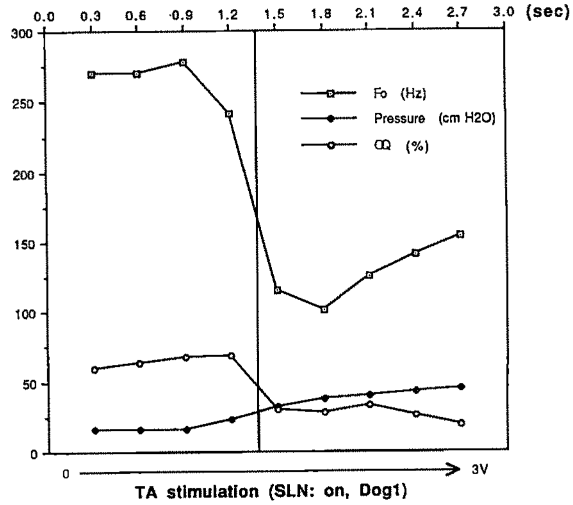

Fig 7. Representative dynamic trial from individual dog. SLN stimulation is present. Fundamental frequency (F0), subglottic pressure, and open quotient (OQ) were measured every 0.3 second while intensity of TA stimulation varied dynamically from 0 to 3 V in 3 seconds. In this plot, y-axis represents units for each variable. Time is on x-axis. Vertical line—sudden shift from high frequency to modal phonation.

was more pronounced. Human EMG data[3,7] suggest that register is regulated primarily by the vocalis muscle, although register, pitch, and intensity are not independent parameters in normal human phonation. Register shifts from falsetto to modal have been associated with increasing vocalis muscle activity. Our data support the suggestion that the TA muscle is responsible for sudden downward frequency shifts.

In the static study, there was a definite decrease in F0 from the TA stimulation-absent condition (high pitch) to the low-TA stimulation condition (modal; Fig 6). Similar results were produced in the dynamic study when SLN stimulation was also present (Fig 5A). In contrast, as TA stimulation increased further during modal phonation, F0 increased. These opposing effects of TA activity on F0 control have been reported by several authors.[9-11,18] An explanation may be found in the body-cover hypothesis.[5,8] Hirano[5] suggested that the TA muscle should be able to stiffen the body of the vocal fold while slackening the cover. Titze et al[11,18] refined this argument, suggesting that nonuniform stiffening of adjacent vocal fold tissue creates an uncertainty about the effective stiffness of the vibrating tissue. Nonuniform stiffening presumably occurs most markedly when the vocal fold is allowed to shorten. If the vibrating cross-sectional area is primarily nonmuscular tissue, then the effective stiffness should be lowered by TA contraction. On the other hand, if the vibrating cross-sectional area is primarily muscular tissue, then the effective stiffness could be raised. The F0 would be expected to change approximately as the square root of the effective stiffness (or equivalently, the effective longitudinal tension).

According to this logic, the dual effects of TA stimulation on F0 control in our data can be explained. Figure 7 shows a representative dynamic trial for an individual dog with SLN stimulation present. The starting point (0.9 second) and the ending point (1.8 seconds) of the F0 decrement correlate exactly with the rapid increment of subglottic pressure (0.9 to 1.8 seconds). After 1.8 seconds, subglottic pressure has built up to a certain extent and F0 begins to increase with increasing subglottic pressure. After this point (1.8 seconds), the increase in tension in the muscle outweighs any decrease in tension in the cover that may result from a small decrease in vocal fold length.

Loudness can be controlled through respiratory and laryngeal mechanisms. In this study, the effect of respiratory control can be ignored, because flow was set constantly at 388 mL/s. Isshiki[19,20] postulated that laryngeal control of intensity is dominant for very low pitches and that expiratory muscle control is dominant for extremely high pitches. In modal register, the muscle that exhibits the greatest variation in activity with changes in intensity is the TA; LCA and IA activity increase with vocal intensity, but less consistently than TA activity.[17] Titze suggested that subglottic pressure is the primary variable for control of vocal intensity,[21] and elevation of subglottic pressure also affects F0.[22] In this study, TA activation definitely increased subglottic pressure (Fig 4A,C and Table 1). However, intensity was not simply correlated with subglottic pressure.

As TA stimulation increased, the OQ decreased gradually (Fig 4B and Table 1). The drop in OQ with TA activation has been reported previously in humans.[23] At the point of sudden pitch shift from high to modal, however, rapid changes in OQ were noted (Fig 7). Both the drop in F0 and the sudden drop in OQ (change of the duty cycle) were correlated with the change in vocal quality observed at this point.

Some researchers claim that the TA consists of 2 muscles: the vocalis, which is the most medial part lying adjacent to the vocal cords, and the TA proper, which lies lateral to the vocalis and comprises the main bulk of the muscle.[9,24,25] They suggest that the TA is a complex muscle, and different subcomponents may have different functions. Because the TA muscle is one of the most important muscles for the laryngeal control of phonation and singing, development of a more elaborate in vivo model (possibly incorporating a constant level of subglottic pressure to drive phonation) to further clarify the delicate functions of the TA muscle will be helpful.

CONCLUSION

A modified in vivo canine model was used to clarify the function of the TA muscle in phonation. Results indicated that TA muscle activation is a major determinant in sudden pitch shifts from high frequency to modal phonation. The F0 increased with increasing TA activation in modal register. The F0 decreased with TA activation when the evoked voice was high in F0. This effect was more pronounced in the presence of simultaneous SLN stimulation. Subglottic pressure increased gradually and OQ decreased gradually with TA activation. However, the change in OQ was more abrupt at the point at which sudden shifts in F0 occurred. This phenomenon seems to be related to changes in voice quality during sudden frequency shifts.

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AIR PULSE QUANTIFICATION OF SUPRAGLOTTIC AND PHARYNGEAL SENSATION: A NEW TECHNIQUE

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There are no published studies evaluating the sensory capacity of the region innervated by the superior laryngeal nerve. A normal sensory capacity is important in this area, since hypesthesia or anesthesia of the pharynx and supraglottic larynx may result in dysphagia and aspiration. This often occurs after stroke or after ablative surgery of the pharynx and larynx. Evaluating the efficacy of restorative procedures for supraglottic and pharyngeal sensation is dependent on defining and quantifying the sensory deficit. We have developed a new, noninvasive method to measure sensation in the pharynx and supraglottic larynx. A puff of air — of precisely controlled duration and pressure — was delivered via a flexible telescope to the anterior wall of the pyriform sinus. Surface sensibility was determined according to the psychophysical method of limits by varying air pressure while holding puff duration constant. We conducted 204 trials in 20 healthy adults. The average sensory discrimination threshold was 2.09 ± 0.15 mm Hg. An intraclass correlation revealed excellent consistency ($\hat{R} = .80$). There was no statistically significant difference between the right and left sides. Brief air pulse stimulation is an easy, relatively safe, and reliable method of determining supraglottic and pharyngeal sensory discrimination thresholds.

KEY WORDS — air pulse stimulation, dysphagia, larynx, pharynx, sensory capacity, superior laryngeal nerve.

INTRODUCTION

The purpose of this paper is to introduce a new, noninvasive method and device that will allow in-office evaluation and documentation of the sensory apparatus in the laryngopharynx. There are no published studies of supraglottic and pharyngeal sensation in normal, healthy individuals, the elderly, or those who have suffered a cerebrovascular accident. Knowledge of pharyngeal and supraglottic sensory discrimination thresholds is particularly important since hypesthesia or anesthesia in this area of the head and neck can cause severe dysphagia and an increased frequency of aspiration. Dysphagia and aspiration are commonly seen in the elderly,[1] in those who have suffered a stroke,[2] and in patients who have had ablative cancer surgery of the pharynx and larynx[3,4] and/or loss of cranial nerves. The evaluation of the efficacy of treatment modalities that address the sensory deficits in the pharynx and larynx is dependent on defining and quantifying the sensory deficits in this region. The first step toward this goal is to establish normal thresholds for sensory discrimination.

There are 2 major problems with measuring sensation in this region of the pharynx and supraglottic larynx, which is innervated by the superior laryngeal nerve. First, mechanical stimulation of pharyngeal and supraglottic mucosa produces a gag reflex. Second, the supraglottic larynx and pharynx are difficult to access, especially in awake patients. These obstacles preclude standard sensory discrimination tests such as static and moving 2-point discrimination, vibratory testing, and stereognosis.[5]

Since no previous method of sensory testing of the supraglottis and pharynx has been described, we have reviewed multiple methods used to test sensation in other parts of the body. Attention was focused on methods that used air puffs, because for the skin, this stimulus is particularly effective in activating cutaneous mechanoreceptors.[6,7] Moreover, compressed air is readily available. Air pulse stimulation of the cornea, or pneumatic tonometry, has been used by ophthalmologists for more than 2 decades to measure intraocular pressure.[8] Sensory discrimination testing using this technique, however, has not been applied to the cornea. On the other hand, brief air pulse stimuli have been used as a natural mechanical stimulus to study the mechanisms whereby the somatosensory system analyzes stimulus patterns.[6,9] Furthermore, air pulse stimuli have been shown to be an extremely sensitive and reliable method of determining sensory discrimination thresholds in the upper

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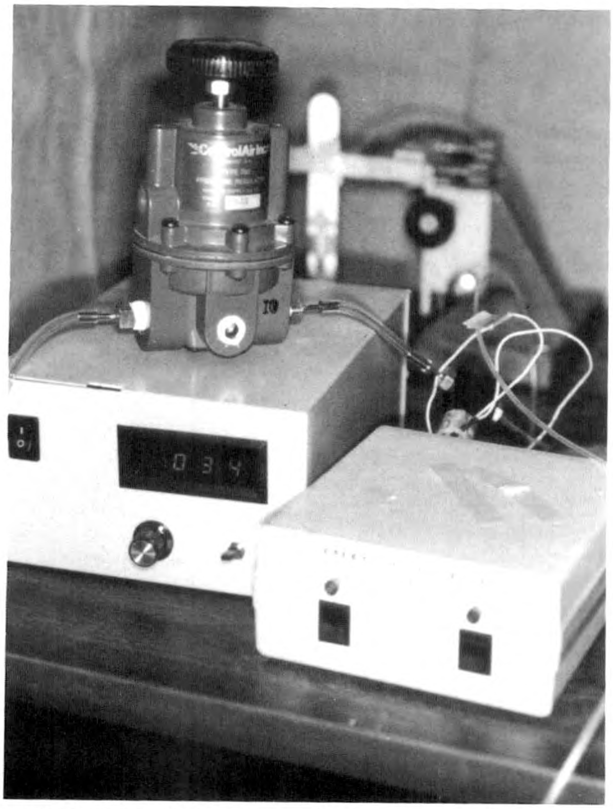

Fig 1. Air puff triggering mechanism consists of components that precisely trigger air puff and includes circuit board, above which are resting pressure regulator and valve driver.

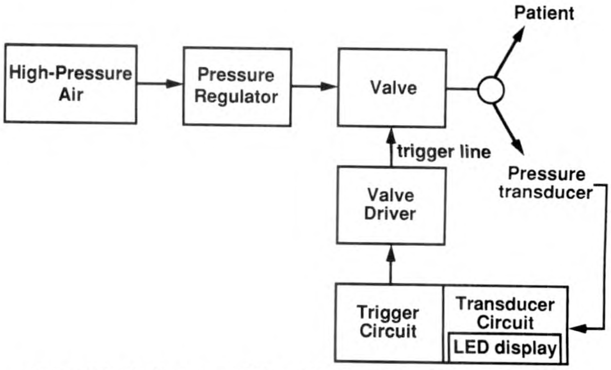

Fig 2. Block diagram of air puff stimulator. For production of strength- and duration-controlled air puff stimuli, output pressure of air source is regulated and led to 2-way valve. Duration of stimulus is determined by open time of valve, which is controlled by trigger gating signal of variable duration. Airflow from valve output is split; 1 side is led to fiberoptic telescope, which is then placed into subject, and other is led to pressure transducer. Transducer output is amplified, and peak voltage change associated with air puff is detected and displayed.

extremity of humans.[6,7] With the concept of discrete air puff, a study was designed to evaluate a method of pharyngeal and supraglottic sensory testing that circumvents the problems of gag and access using a newly developed, noninvasive device. The nature of the stimulation from a puff of air is different from the usual physiologic stimulation to the supraglottis. There exist no other tests of any kind to measure sensation in this region. Furthermore, there are no data to suggest that the pharyngeal and supraglottic sensory response to food and saliva is different from that to a puff of air.

MATERIALS AND METHODS

The psychophysical method of limits was used to determine the sensory capacity of the pharynx and supraglottic larynx in 20 healthy adults, 12 men and 8 women, ranging in age from 24 to 78 years with a mean of 44 years. To measure supraglottic and pharyngeal sensory level, a pressure- and duration-controlled puff of air was delivered via a secondary port located within a standard flexible fiberoptic telescope (Pentax Precision Instrument Corporation, Orangeburg, NY) to the anterior wall of the pyriform sinus. Air pressure was varied and sensory thresholds were determined according to the psychophysical method of limits, while the duration of the air puff was held constant at 50 milliseconds. This puff duration of 50 milliseconds was chosen because after multiple trials it was noted to be the briefest puff of air that would give a just-noticeable change in the pharyngeal sensory discriminatory ability of test subjects. The duration and pressure of the administered air puff were controlled by an electronic valve, a pressure gauge, and a pressure sensor that was used to monitor the pulse (Fig 1).

The air puff was obtained from the standard air pump found in most otolaryngology offices for the delivery of aerosolized medications (SMR Maxi Cabinets, Storz Surgical Specialties, St Louis, Mo). Each week the air pump was calibrated by a pressure gauge that was attached to the pump. To deliver air pressure to the test site in the pharynx and larynx, small-diameter, flexible polyethylene tubing was attached to the fiberoptic telescope. To measure the amount of air pressure that was being delivered to the test site in the pharynx, an identical length of polyethylene tubing was attached via a Y-connector to a pressure sensor (Motorola, Inc, Phoenix, Ariz).

The nose was anesthetized with 1% Xylocaine with epinephrine 1:100,000 that was placed on a cotton-tipped applicator and passed along the nasal septum for a distance of 1 cm from the nasal vestibule. No other anesthesia was given. The applicator was removed and a flexible fiberoptic telescope was passed via the nose, and the distal tip was advanced until it was located 2 mm from the test site. The distal tip of the air tubing used to monitor the pulse was also fixed at 2 mm from the pressure sensor device. In this manner the exact pressure being delivered to the patient was simultaneously being delivered to the

SUPRAGLOTTIC SENSORY DISCRIMINATION THRESHOLDS

Age (y)	*N*	*Mean ± SD*
20-30	5	2.03 ± 0.14
31-40	7	2.06 ± 0.10
41-50	1	2.10 ± 0.80
Mean		2.06 ± 0.11*
51-60	0	
61-70	2	2.25 ± 0.08
71-80	5	2.40 ± 0.04
Mean		2.34 ± 0.07
Total	20	2.09 ± 0.15

Means include measurements from both right and left sides. Data are in millimeters of mercury.

*p < .0001.

pressure sensor (Fig 2). While there was likely up to a millimeter's variation in the distance the telescope was placed from the target site, by bracing the scope with the examiner's gloved fingers against the test subject's nose a consistent distance from the target site in the pyriform sinus was achieved.

Procedure. Each test subject was provided a detailed description of apparatus and procedure and signed a consent form. This project was approved by the Columbia University Institutional Review Board. The subject was given the opportunity to feel an air puff on the cheek and to discuss the sensation with the investigator. Next, the flexible telescope was inserted into the nasal passage and the subject was given a 1-minute rest period to adapt to the laryngoscope and prepare for testing. The testing procedure began by orienting the subject to the stimulus by means of a suprathreshold stimulus of 5 seconds' duration. This stimulus is 100 times stronger than the test air puff. After a 15-second rest period, 6 blocks of stimulus administration trials were given. Each trial lasted for approximately 10 seconds, with a 10-second intertrial interval. The air puff was administered at a random time from 2 to 8 seconds within the 10-second trial interval after a verbal announcement of the beginning of the trial. A detection response occurred when the subject raised his or her hand within 2 seconds after stimulus presentation. Three blocks of descending pressure stimulus presentations and 3 blocks of ascending pressure stimulus presentations were randomly ordered for each subject. Within a block, air puffs were presented in sequential steps of 10 test unit changes (each unit is equivalent to 7.5×10^{-3} mm Hg): from subliminal to supraliminal for ascending blocks and from supraliminal to subliminal for descending blocks. A 30-second rest period separated each block. The mean of the lowest detected pressures from each of the 6 blocks was used as that subject's sensory threshold. Both the right and left sides of the pharynx and supraglottic larynx were studied.

All testing was performed by 3 of the investigators (J.E.A, M.S.K., A.B.) over a 1-year period. Each subject was tested at least twice over this time period. To look at the consistency and reliability of sensory discrimination ratings with this device and technique, multiple testings of the same subjects were carried out. Specifically, 3 subjects were tested 4 times over a 3-month period, and 1 subject was tested 7 times over a 1-year period.

STATISTICAL ANALYSIS

To determine differences between right and left sides, Student's *t* test was used. One-way analysis of variance was used to assess age-related changes in pharyngeal and supraglottic sensation. An intraclass correlation was computed to determine the reliability of this device and technique.

RESULTS

A total of 204 trials were conducted in the 20 test subjects. The age breakdown of the subjects by decade is located in the Table. For the entire population studied, supraglottic and pharyngeal sensory pressure thresholds were, on the average, 2.09 ± 0.15 mm Hg. Testing for normality revealed a normal distribution of data points. Student's *t* test showed no statistically significant difference between the right and left sides. An intraclass correlation revealed excellent consistency ($\hat{R} = .80$).

Seven of the 20 subjects studied were over 60 years of age. Age-related changes in supraglottic and pharyngeal sensory discrimination thresholds were found to be statistically significant ($p < .0001$). Patients over 60 had a sensory discrimination threshold of 2.34 ± 0.07 mm Hg, while patients less than 60 had a sensory discrimination threshold of 2.06 ± 0.11 mm Hg (see Table).

At suprathreshold sensory pressure levels, air puff stimulation generally resulted in gagging by the subject. Repeat sensory testing after gagging revealed that sensory pressure thresholds were unchanged.

In the 204 trials there were absolutely no adverse reactions to the sensory testing procedure. In particular, there were no episodes of epistaxis, infection, or airway compromise.

DISCUSSION

We have used basic principles of air puff stimulation and developed a new technology and an in-office method to noninvasively assess supraglottic and pharyngeal sensation. The stimulation system enables the user to deliver a brief puff of air, the duration and amplitude of which can be precisely controlled, and to monitor the strength of the puff with a light-emitting diode display. In 204 trials in 20 subjects, our new method has been found to be easily and reproducibly performed, relatively safe, and statistically accurate. The duration of testing was on the average no more than 10 minutes longer than the time it took to perform a typical flexible fiberoptic laryngoscopy.

There was a statistically significant increase in sensory thresholds of persons older than 60 years. Studies on aging and sensation have established that with increasing age, sensory discrimination in the oral cavity diminishes.[10,11] This correlates with the fact that as one gets older, aspiration during swallowing is more likely to occur.[1,12] The only explanation for this increased incidence of aspiration is dysfunction of oral and pharyngeal motor control, such as abnormal lingual activity, poor lingual-palatal seal, and pharyngeal pooling. The results of the present study raise the possibility that pharyngeal and supraglottic sensory abnormalities might contribute to the development of aspiration.

It is our hypothesis that supraglottic and pharyngeal sensory discrimination thresholds are increased progressively with age. This sensory deficit may compound the known motor deficits, thus playing a significant role in the development of dysphagia and/or aspiration in these patients. Future work will be directed toward further evaluating these suppositions.

CONCLUSION

We have developed and tested a relatively safe and statistically effective method and device to assess quantitative sensation in the supraglottic larynx and pharynx. Our study suggests age-related sensory changes. Further studies are needed to determine the relationship between age-related changes in supraglottic and pharyngeal sensory discrimination and the development of dysphagia in the elderly. The testing method that we have developed is an objective and reproducible means to evaluate sensory capacity in the supraglottic larynx and pharynx and should help to assess the efficacy of the rehabilitation of patients with dysphagia and/or aspiration.

ACKNOWLEDGMENTS — The authors thank Dr Beverly Diamond and Donald McMahon of the Columbia-Presbyterian Irving Center for Clinical Research for their invaluable expertise in statistical analysis.

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Ann Otol Rhinol Laryngol 102:1993

HAIR RELAXER INGESTION: A NEW TREND

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Although the health care system has done much to reduce the incidence of ingestion of such alkalis as drain and oven cleaners, in recent years we have seen an overwhelming increase in the incidence of hair relaxer ingestion. In a 5-year review (1987 to 1992) of 48 cases of caustic ingestion, 15 cases involved alkaline hair-relaxing agents. This retrospective study was undertaken to evaluate the agents ingested, the presenting signs and symptoms, the diagnostic procedures, and the outcomes in those 15 cases. Oral cavity and lip burns were common in these children, but none of the 15 had significant esophageal burns. Education of the medical and lay community about the risk of hair relaxer ingestion should be undertaken to reverse this worrisome trend.

KEY WORDS — caustic ingestion, esophageal stricture, esophagoscopy, hair-relaxing agent.

INTRODUCTION

Despite numerous medical and legislative advances, caustic ingestion remains a challenging and controversial pathologic entity. In treating caustic ingestion, the modern era began in the United States with Chevalier Jackson's development of the end-lighted esophagoscope in response to a growing number of pediatric lye ingestions. His lobbying efforts culminated in 1927 with the passing of the Federal Caustic Act, which provided for the poison labeling of caustic products.[1] Surgical and dilation techniques for the treatment of esophageal stricture improved throughout the first half of the century, and steroid therapy became popular in 1950 after the work of Spain et al.[2] The Federal Hazardous Substance Labeling Act in 1960 was followed by the Safe Packaging Act in 1970. The first highly concentrated liquid alkali cleaning agents came on the market in 1967 and resulted in a significant increase in the number of severe esophageal burns. This prompted the federal regulation of liquid alkali products to a concentration not greater than 10%.[3]

Nonetheless, the incidence of caustic ingestions remains high. The US Poison Control Centers estimate that 26,000 caustic ingestions occur per year, with 17,000 occurring in children.[4] There is a bimodal distribution, with a second group consisting of suicide gestures and suicide attempts in older patients.[5]

Caustic agents are generally considered to be substances that can cause mucosal burns of the aerodigestive tract. Alkaline products account for the majority of ingestions and for the greatest number of serious injuries.[5] These products include lye, miniature batteries, and Clinitest tablets. Acid ingestion is the second most common cause of severe burns. Ammonia, chlorine bleach, and detergent ingestions, although common, are rarely responsible for significant morbidity. Hydrochloric acid, sulfuric acid, and swimming pool chemical ingestions can be more dangerous.

Alkaline agents cause a rapid, deep liquefactive necrosis when they contact gastrointestinal mucosa. Even short exposure to an agent with a pH of 12.5 or greater may result in a significant burn. Howell[6] reports that although first-degree injuries do not progress to stricture, approximately 15% to 30% of second-degree burns will cause esophageal stenosis, and more than 90% of third-degree burns will result in clinically significant stricture. The probability of causing damage is generally thought to be greater with liquid agents than with solid ones,[6,7] but this is controversial.[5]

In contrast to alkalis, acids cause a coagulation necrosis whereby the coagulum reduces further penetration of the agent into the muscle layers. Acids are therefore less likely than alkalis to cause severe esophageal burns. The most significant complications occur in the gastroduodenal region.

The factors determining the toxicity of a caustic agent are debatable. Vancura et al[8] examined alkaline solutions and suggested that pH measurement is the best indicator for determining initial management of ingestions and that the critical pH for esophageal ulceration is 12.5. Viscosity was not felt to be clinically useful. In a more sophisticated study, Hoffman et al[9] found that the titratable acid or alkaline reserve of a caustic agent correlated better than pH with the production of esophageal injury.

The procedure of choice for diagnosis of upper

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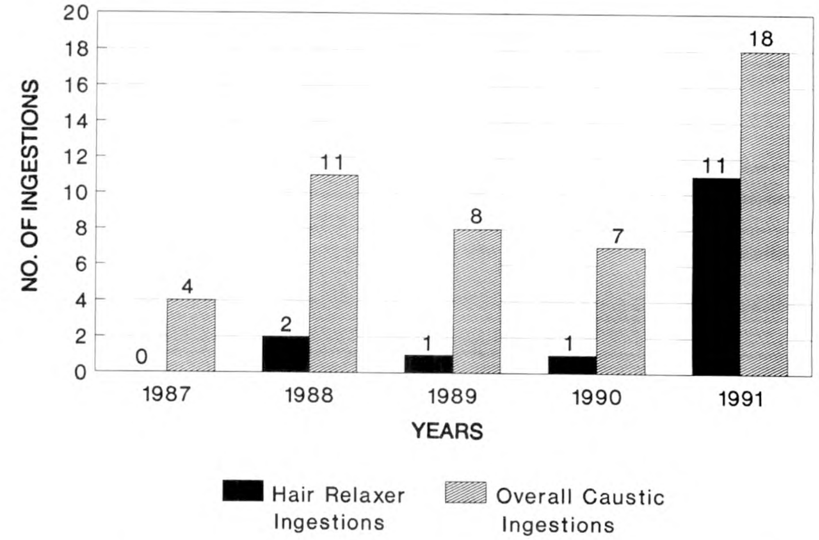

Fig 1. Number of hair relaxer ingestions versus number of overall caustic ingestions per year.

aerodigestive tract injury after caustic ingestion is esophagoscopy. This is a relatively low-risk, inexpensive procedure that is quite sensitive in detecting those burns that may later become clinically significant. No procedure, however, is without risk, and the cost of performing esophagoscopy in all cases of caustic ingestion would be high. To avoid unnecessary esophagoscopy, several authors have attempted to identify signs and symptoms that are predictive of second- and third-degree esophageal burns. There is no consensus, however. Neither Gaudreault et al[10] nor Gorman et al[11] found a single sign or symptom predictive of severe burns. Vomiting, dysphagia, drooling, and abdominal pain were, however, more frequently associated with severe burns than were other signs and symptoms.[10] Crain et al[12] compared the incidence of vomiting, drooling, and stridor with esophagoscopy findings, reporting that half of those patients with 2 or more of these signs had second- or third-degree burns. No positive endoscopic results were found in patients with none or only 1 of these clinical findings. The presence of oropharyngeal burns was not predictive of severe esophageal burns.[12] Previtera et al[13] concurred. These studies support the practice of diagnostic esophagoscopy in all symptomatic cases of caustic ingestion other than those involving bleach.

At St Louis Children's Hospital, a tertiary-care referral center and part of the Washington University Medical Center, an increase was noted in the number of cases of hair relaxer ingestion. These products are alkaline and often contain lye. A 5-year retrospective review of these cases is reported.

METHODS

Of the 48 patients admitted to St Louis Children's Hospital between 1987 and 1992 for caustic ingestion, 15 had ingested a hair-relaxing agent. Each patient was initially evaluated in the emergency department by a pediatrician and a physician from the otolaryngology or pediatric surgery service. The following data were recorded for each case: patient age, race, home status (single-parent or 2-parent household), and insurance status (private versus welfare or uninsured).

All 15 patients were hospitalized and given intravenous hydration. No patients received steroids, although 4 were given intravenous antibiotics (penicillin or a cephalosporin). Barium swallow examination and/or esophagoscopy was performed 12 to 24 hours after ingestion. Rigid esophagoscopy was performed by a staff member from the otolaryngology service. Evaluation of gastrointestinal burns was based on the conventional system, with first-degree burns showing mucosal erythema or edema, second-degree burns showing mucosal ulceration, and third-degree burns showing deep ulceration, necrosis, or perforation. Routine follow-up within 4 weeks of discharge was ordered. Telephone follow-up was attempted for all patients who had ingested hair relaxer.

Finally, 8 commercially available hair-relaxing agents were purchased. The pH of each agent was determined with pHydrion Mikro strips (Micro Essential Laboratory, Brooklyn, NY).

RESULTS

Between 1987 and 1992, 48 cases of caustic ingestion were seen at St Louis Children's Hospital, and of these, 15 (31%) involved the ingestion of a hair-relaxing agent. There was a marked increase in the number of caustic ingestions, particularly of hair relaxers, in 1991 (Fig 1). The mean age of the patients was 16 months, with a range of 10 months to 26

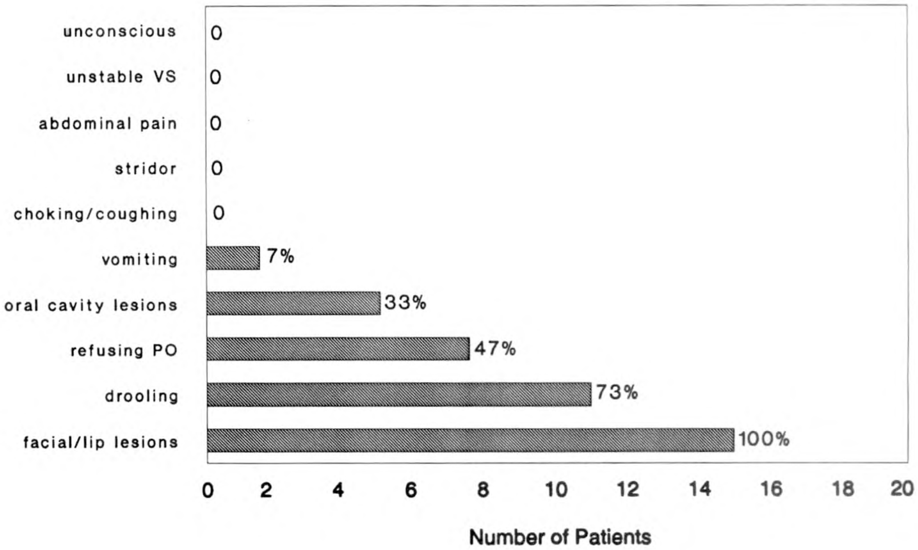

Fig 2. Presenting signs and symptoms of patients ingesting hair relaxers (n = 15). VS — vital signs, PO — oral feeding.

months. All 15 patients were black. One patient came from a 2-parent household, while 14 of 15 (93%) patients were from single-parent homes. Four patients had private insurance, while 11 of 15 (73%) were either on welfare or uninsured.

The presenting signs and symptoms of those patients admitted for ingestion of hair relaxers are shown in Fig 2. All patients presented with facial or lip lesions (usually swollen, erythematous lips). Seventy-three percent of the patients exhibited drooling, 47% refused to take milk or water offered in the emergency department, and 33% had oral cavity lesions (first- or second-degree burns).

All 15 patients underwent diagnostic procedures. Of the 6 patients (40%) who underwent barium swallow examination, only 1 displayed esophageal mucosal irregularity. This patient then underwent esophagoscopy that subsequently ruled out the presence of any true lesion. Ten patients (67%) underwent rigid esophagoscopy to the gastroesophageal junction. Three patients (20%) were found to have mild erythema and/or edema at several sites in the proximal aerodigestive tract, but none was found to have a severe esophageal burn (second- or third-degree). There were no complications from the barium studies or esophagoscopy.

The mean hospital stay for these patients was 2.2 days, with a range of 1 day to 3 days. No patient received any form of treatment after discharge from the hospital. Telephone follow-up was successful in 9 patients (60%). Time of follow-up after patient discharge ranged from 6 months to 4 years. There was no report of significant clinical sequelae from the ingestion at the time of follow-up.

All hair-relaxing agents assayed had a pH between 12.5 and 13.0. Sodium hydroxide or calcium hydroxide was the active ingredient.

DISCUSSION

Caustic ingestion continues to be a serious problem in the pediatric population. Our small series reports a rising trend in the ingestion of hair-relaxing agents, potent alkaline products. This trend may reflect an increased usage of such products within the black community.

This study found no severe burns of the upper aerodigestive tract after hair relaxer ingestion, but the sample size was quite small. The pH of these products certainly has the capability to severely damage esophageal mucosa,[8] with consequent potential for serious morbidity.

Although all of the products investigated had some warning on the container, nearly half of these had no specific admonition to keep the product out of the reach of children. All but 1 of the products were labeled "For professional use only," but were readily available commercially. Child-proof packaging and specific warning levels should be mandated. Education of the lay community and physicians about the danger of these products is also imperative.

Evaluation and treatment of hair relaxer ingestion should follow the protocol for all concentrated alkaline products. Careful history-taking and physical examination in the emergency department is mandatory. Dilution with milk or water may be helpful, as is copious irrigation of all visible lesions. Patients should be admitted for observation, with esophagoscopy to follow within 12 to 48 hours. Barium swallow examination may be less helpful because of frequent false-negative readings, but we have occasionally elected to use this in burns that seem significantly less symptomatic.[3] Steroids and antibiotics are beneficial for moderately severe burns. Stricture formation that follows severe circumferential burns will probably be unaffected by steroids. Patients should be seen for office follow-up at 2 to 4 weeks, with barium swallow examination reserved for those with second- and third-degree burns.

We noted that the majority of hair relaxer ingestion cases occurred in young children from single-parent, underprivileged households. These are often stressful environments with numerous complicating socioeconomic factors. Treating physicians should have a low threshold for involving social services in the care of these patients and their families.

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EXTRACRANIAL OPTIC NERVE DECOMPRESSION

A meeting to discuss extracranial optic nerve decompression as a treatment for traumatic optic neuropathy will be held November 6-7, 1993, at Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. For information, contact Michael Joseph, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3096; telephone (617) 573-3192; fax (617) 573-3914.

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DEDIFFERENTIATED CHONDROSARCOMA OF THE LARYNX WITH REGIONAL AND DISTANT METASTASES

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Chondrosarcoma of the larynx is an unusual tumor, with only approximately 200 cases having been reported. This tumor is relatively nonaggressive and tends to remain localized in the larynx. Two cases with aggressive clinical behavior manifested by regional or distant metastasis are presented. In the first case, cervical node metastasis appeared 6 months after total laryngectomy. A dedifferentiated chrondrosarcoma was identified by pathologic examination. In the other case, clavicular metastasis developed 7 years after initial local excision. Despite additional treatments, the patient later developed cervical node, lung, and vertebral metastasis. Transformation from low-grade to dedifferentiated chondrosarcoma was verified by pathologic examination. We believe this case to be the first reported laryngeal chondrosarcoma with bone metastasis. A review of the literature regarding regional and/or distant metastasis of laryngeal chondrosarcoma, including the present observations, reveals a total of 20 cases. In all cases, tumor grade has been directly correlated with the development of metastasis.

KEY WORDS — chondrosarcoma, distant metastasis, laryngeal neoplasm, larynx, regional metastasis.

INTRODUCTION

Sarcomas of the larynx are rare; they have accounted for fewer than 1% of laryngeal cancers.[1] Chondrosarcoma is by far the most common laryngeal sarcoma. In 1984, Ferlito et al[2] reviewed 149 cases of laryngeal chondrosarcoma. Later, Nicolai et al[3] reviewed an additional 50 cases from the medical literature, including 5 of their own. These 204 cases of reported laryngeal chondrosarcoma are the only ones known in the literature.

Unlike the other head and neck chondrosarcomas, laryngeal chondrosarcoma is relatively low grade, both in histology and clinical aggressiveness.[4,5] This tumor tends to remain localized in the larynx during its clinical course. It seldom manifests metastasis to regional or distant sites. To date, 18 cases with regional and/or distant metastasis have been reported in the literature.[2,3,6-22] The incidence has been estimated as 8% to 14%[2,3,23] of all laryngeal chondrosarcomas.

In the last 20 years, we in the Otolaryngology Division at the University of Wisconsin Hospital and Clinics have had experience with 2 cases of metastasized laryngeal chondrosarcoma. In this paper we present these 2 rare cases: 1 associated with regional lymph node metastasis, and the second with clavicular, vertebral, pulmonary, and regional lymph node metastasis. We believe the latter case to be the first reported laryngeal chondrosarcoma with bone metastasis.

We also present a brief review of the literature regarding regional and/or distant metastasis of laryngeal chondrosarcoma, in which we correlate tumor grade with the development of metastasis.

CASE REPORTS

Case 1. A 58-year-old woman was first seen in a local clinic; she had a 4-month history of progressive hoarseness and dyspnea. Evaluation revealed a subglottal tumor mass that required an emergency tracheotomy for increasing dyspnea. Biopsy revealed a dedifferentiated chondrosarcoma. She was then referred to our clinic in April 1971. At the time of admission the patient stated there was no localized pain, odynophagia, or dysphagia. She smoked less than 1 pack of cigarettes per day and denied alcohol use. In the larynx, a pinkish red mass was seen just posteriorly, inferior to the right vocal fold. It appeared to occlude most of the visible airway beneath the true vocal folds. Both vocal folds appeared to move well; no masses were palpated in the neck. Because of the tumor size, histologic findings, and the rapid growth of the tumor during the previous month, the patient underwent a total laryngectomy. During surgery, a 3.5-cm-diameter tumor mass was found to involve and replace the entire posterior

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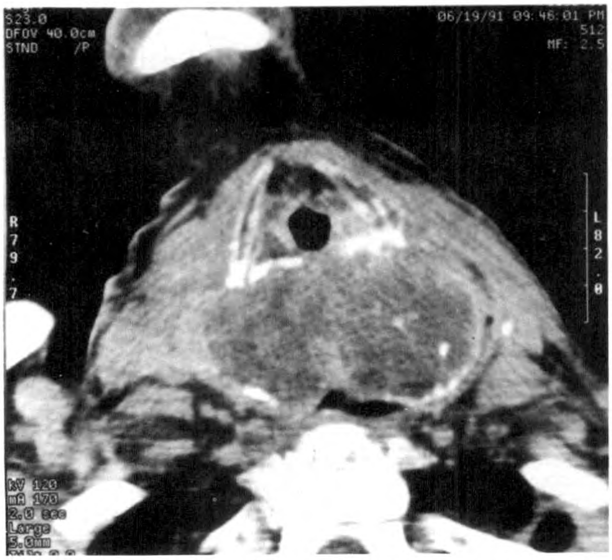

Fig 1. (Case 2) Computed tomogram showing axial section at level of larynx: large tumor mass involving posterior larynx with significantly compromised airway.

lamina of the cricoid cartilage. The patient was readmitted in August 1971 because of a recurrence above the tracheal stoma; this lesion was excised. The next month, she developed another neck mass on the left midjugular chain; this lesion was treated by a neck dissection. The patient remained asymptomatic until May 1976, when she developed a right neck mass; this lesion was also excised. Another 4 regional recurrences ensued during the subsequent 8 years. The patient succumbed in January 1985 to an acute pulmonary embolus unrelated to the primary tumor. An autopsy showed no evidence of distant metastasis.

Case 2. A 62-year-old man was first seen in our clinic in December 1983 with a 2-year history of progressive dyspnea and dysphagia. The patient manifested an obvious stridor on inspiration and expiration. He denied any odynophagia or hoarseness. He did not smoke tobacco or drink alcohol. In the larynx, a marked submucosal mass was visualized posteriorly in the subglottic area. The subglottic airway was approximately one third of its normal diameter. Both vocal folds appeared to move well; no masses were palpated in the neck. The patient underwent a tracheotomy followed by a tumor excision through a laryngofissure. An obvious tumor mass was found to involve the cricoid cartilage on the left side. It partially extended to the left true vocal fold posteriorly. The tumor was excised, with a sufficient laryngeal framework remaining for a later reconstruction procedure. The patient remained asymptomatic until September 1986, when a follow-up computed tomography (CT) scan revealed a recurrent mass in the posterior portion of the cricoid cartilage. A total laryngectomy was advised, but the patient refused further treatment. In June 1991, however, the patient was readmitted because of difficulty in breathing. He also reported hemoptysis and hoarseness. A CT scan revealed a 7 × 4 × 4-cm mass in the prevertebral space, with compression of the posterior hypopharynx (Fig 1). At the same time it was found that the patient had a left distal pathologic fracture of the clavicle. It was suspected that this fracture had resulted from tumor metastasis (Fig 2). The patient underwent a total laryngectomy and a wide excision of the left distal clavicle (Fig 3). The patient developed a left-sided neck mass 3 months later. The mass could not be completely removed because of its extension toward the skull base and the thoracic inlet. During that admission the patient was found to have both a pulmonary metastasis and a T-8 vertebral body metastasis (Fig 4). The vertebral lesion was treated with palliative irradiation. The patient later developed further metastasis in the left anterior chest wall;

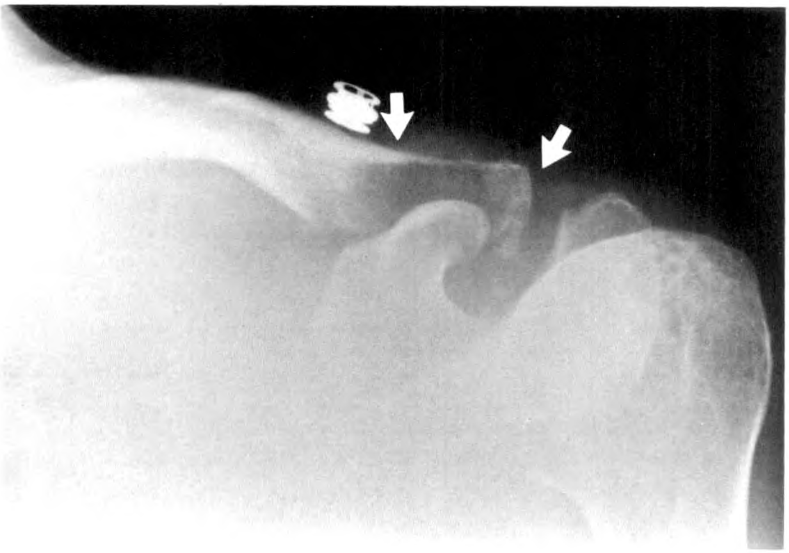

Fig 2. (Case 2) Plain radiograph of left shoulder. Shows osteolytic lesion involving distal clavicle with pathologic fracture (arrows).

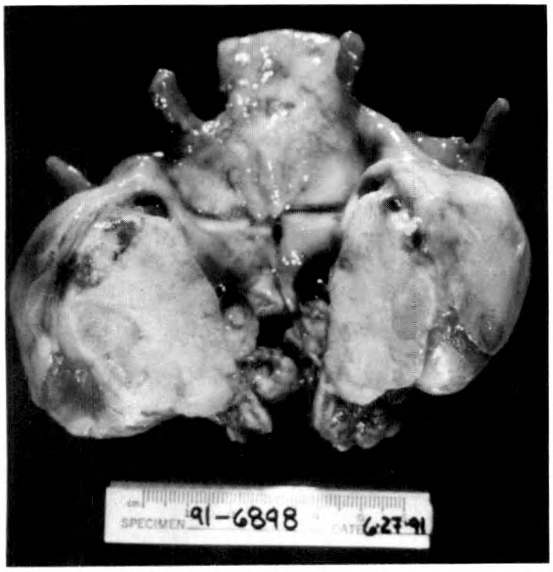

Fig 3. (Case 2) Laryngectomy specimen opened posteriorly. Large, lobulated tumor mass arises from posterior portion of thyroid cartilage.

this lesion was also irradiated. The patient is currently being followed up by his local physician, and continues to live with persistent disease.

PATHOLOGIC FINDINGS

Case 1. Gross examination of the surgical specimen (primary tumor, total laryngectomy) revealed a tumor, 2.5 cm in diameter, that replaced the entire posterior portion of the cricoid lamina. Microscopically, the tumor was covered by a pseudostratified columnar epithelium and composed of numerous lobules of cartilaginous tissue. Within these lobules, some areas indicated a well-differentiated cartilaginous tissue (grade 1) with small chondrocytes and a well-developed chondroid matrix. Other areas had a moderately differentiated cartilaginous tissue (grade 2) with increased cellularity and larger nuclei. In some other areas, the tumor nodules showed poorly differentiated cartilaginous tissue (grade 3) with dense cellularity, spindle cell changes, and increased mitotic figures (Fig 5). This grading was based on the system described by Evans et al.[24]

The metastatic lymph node mass (regional metastasis, left radical neck dissection) was 3 × 2 × 2 cm. Sectioning revealed granular, fleshy tissue and a necrotic portion that included one third of the specimen. Microscopically, the metastatic tissue manifested more undifferentiated changes with increased nuclear atypia and mitotic figures than were evident in the primary tumor.

The histologic appearance of the subsequent regional metastases resembled that of the initial lymph node metastasis.

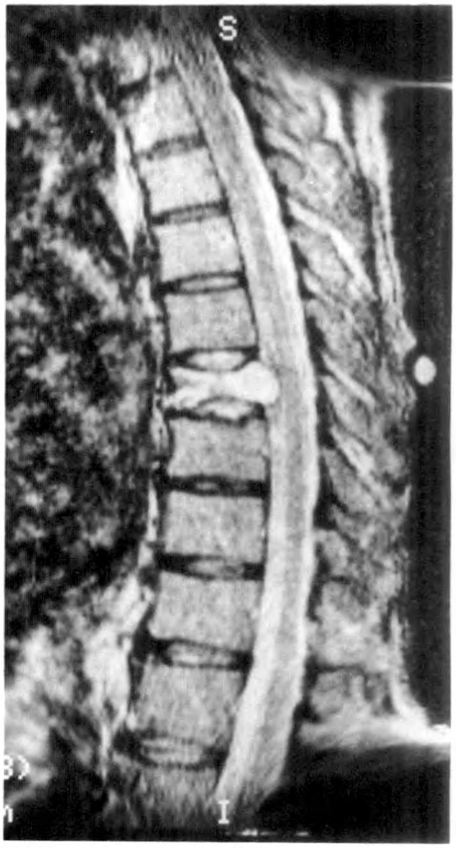

Fig 4. (Case 2) T2-weighted magnetic resonance image of thoracic spine showing compression fracture of T-8 vertebral body with posterior protrusion on spinal cord. S — superior.

Case 2. Gross examination of the surgical specimen (primary tumor, laryngofissure procedure) revealed firm, rubbery, white-gray tissue. Microscopically, the tumor was a well-differentiated or low-grade (grade 1) chondrosarcoma composed of chondrocytes with small dark nuclei and a well-developed chondroid matrix. Mitotic figures were not found.

Gross inspection of the surgical specimen (local recurrence, total laryngectomy) indicated an 8 × 5.5 × 5-cm tumor mass that apparently arose from the posterior portion of the thyroid cartilage. The cut surface of the tumor was white-gray in color, firm, fleshy, and cartilaginous in appearance (Fig 3). Microscopically, the tumor showed portions of conventional chondrosarcoma (grade 1) blending into areas of high-grade sarcoma (grade 3). The areas of high-grade sarcoma had numerous mitotic figures, multinucleated tumor giant cells, and anaplastic spindle-shape cells resembling pleomorphic malignant fibrous histiocytoma (Fig 6A). These findings were a remarkable contrast to the low-grade chondrosarcoma found in the patient's primary tumor when it had been removed approximately 7 years before.

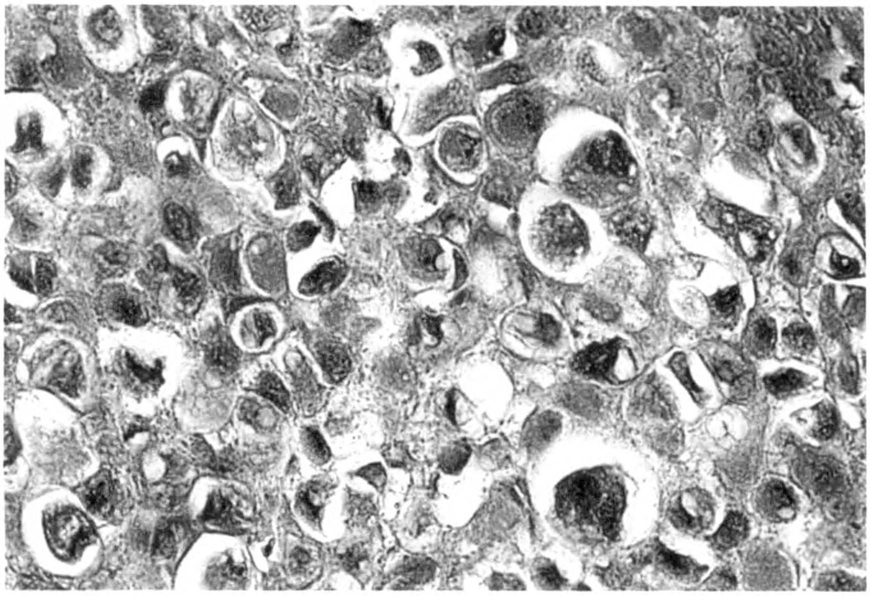

Fig 5. (Case 1) Poorly differentiated portion (grade 3) of dedifferentiated chondrosarcoma (H & E, original x400).

The tip of the clavicular head (distant metastasis, clavicle excision) was replaced by a whitish yellow, gelatinous soft tumor mass that eroded into and weakened the cortex. Microscopically, the tumor consisted only of high-grade sarcoma tissue (grade 3) that resembled the high-grade portion of the previous, dedifferentiated chondro-sarcoma (Fig 6B).

DISCUSSION

Histopathologic Context of Chondrosarcoma. Cartilage is a specialized form of connective tissue in which the chondrocytes synthesize and secrete an extracellular matrix. This matrix gives cartilage a firm consistency and endows some of its unique and crucial functions such as the support of soft tissue, the resistance to mechanical stress, and the development of long bones.[25] The malignant change of chondrocytes is known as chondrosarcoma, which accounts for 10% to 20% of all malignant primary bone tumors.[4] Chondrosarcomas generally arise from the pelvis or the extremities. Only approximately 10% arise from the head and neck area.[4] The paranasal sinuses, nasal cavity, temporal bone, mandible, and larynx are the most commonly involved sites of head and neck origin.[4,5] The histologic spectrum of chondrosarcomas varies from a well-differentiated growth that can be similar to a benign cartilage tumor, to a high-grade malignancy that exhibits aggressive local behavior and potential for metastasis.[5]

In 1943, Lichtenstein and Jaffe[26] developed specific histologic criteria for determining the benignity or malignancy of cartilaginous tumors. They stressed the importance of examining the characteristics of the cells and observing the viable and noncalcifying areas of the lesion to avoid underdiagnosis of the tumor. In spite of these guidelines, the distinction between chondroma and grade 1 chondrosarcoma is very difficult. In laryngeal cartilaginous tumors[27] such distinctions should probably not be made.

The notion that higher–histologic grade tumors are associated with shorter survival became well recognized in the 1950s.[28] Later, Evans et al[24] statistically correlated the histologic grade of chondrosarcoma of bone with biologic behavior. They based their 1-to-3 grading criteria on mitotic rate, evidence of atypia, and indications of nuclear size and cytoplasmic differences. They found the 5-year survival rates of patients with chondrosarcomas of grades 1, 2, and 3 in all anatomic sites to be 90%, 80%, and 43%, respectively. The metastasis rates were 0%, 10%, and 71%, respectively.

Dedifferentiation of Chondrosarcoma. The term dedifferentiated chondrosarcoma was first introduced by Dahlin and Beabout in 1971.[29] They reported 33 cases of well-differentiated chondrosarcoma of bone with additional malignant mesenchymal components such as fibrosarcoma or osteosarcoma. Some authors[30,31] prefer instead to use the term chondrosarcoma with additional mesenchymal component, because of the morphogenesis of the tumor. This dedifferentiated tumor represents 6% to 10%[29,31] of all chondrosarcomas and frequently involves the extremities, especially the proximal femur and the pelvic bone. The prognosis for this tumor is extremely poor; the average survival duration has been reported as only 6 months,[30] and approximately 70% of patients manifest a pulmonary metastasis during their clinical course.[31] The poor prognosis associated with this type of tumor is attributed to the presence of the ad-

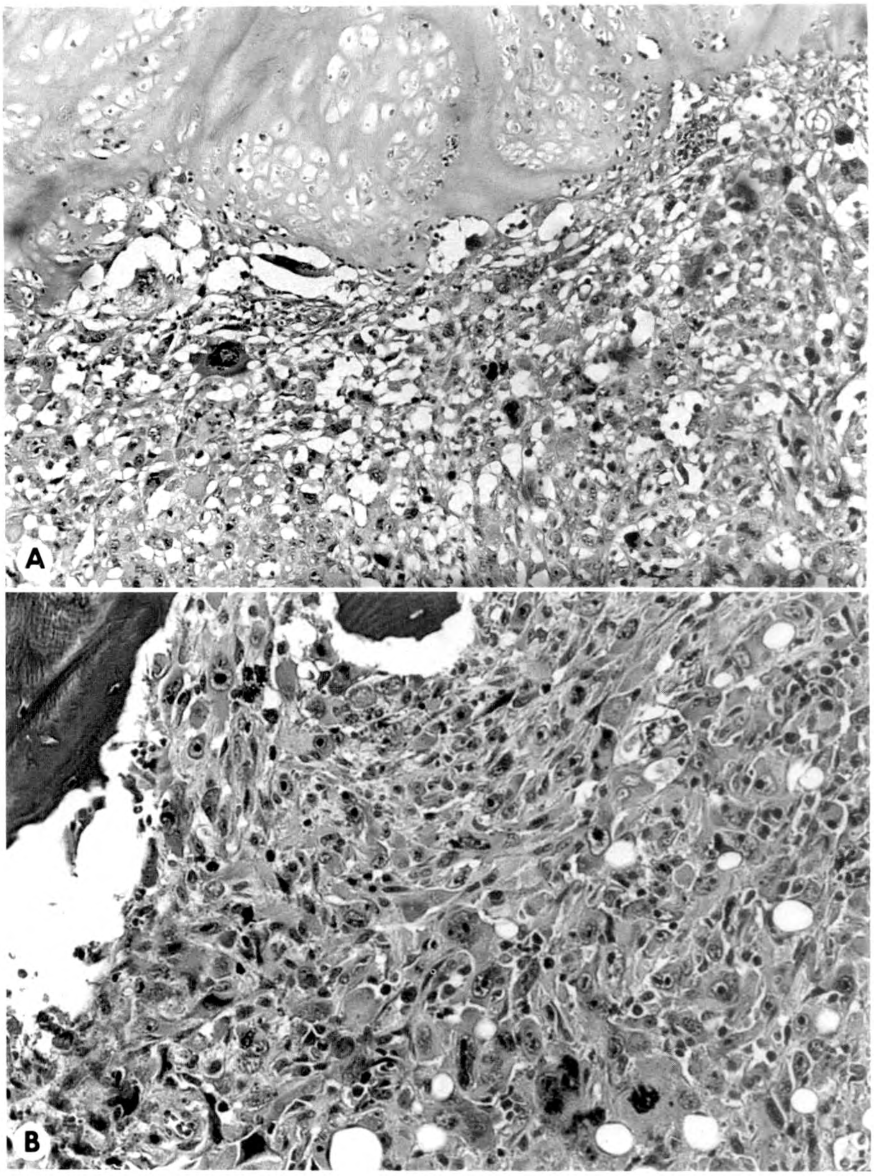

Fig 6. (Case 2) A) Dedifferentiated chondrosarcoma showing interface between low-grade portion (above) and high-grade portion (below; H & E, original x100). B) Bone invasion of high-grade (grade 3) chondrosarcoma (H & E, original x200).

ditional malignant component that has arisen from the preexisting, well-differentiated cartilaginous tumor.[30,32,33]

It is our opinion that the malignant component represents some form of an evolutionary proliferation of tumor cells. The additional malignant component might be fibrosarcoma, osteosarcoma, or malignant fibrous histiocytoma, as in our case 2. Evidence from our case 1, in which the tumor demonstrated dedifferentiation in the initial specimen, is contrasted with our case 2, in which only a well-differentiated tumor was manifested in the initial specimen. A histopathologic transformation was clearly verified in the latter case.

Regional and Distant Metastasis of Laryngeal Chondrosarcoma. A review of the literature regarding regional and/or distant metastasis of laryngeal chondrosarcoma, together with the present cases, has revealed a total of 20 cases (see Table[2,6-22]). The most common site of metastasis was the lung, and the second, the cervical node. Bone metastasis has been reported only in our case 2.

We also reviewed the histopathology of each metastasized tumor. The pathology column of the Table, however, represents some speculation on the part of our senior pathologist (G.R.H.), for previous investigators did not always clearly describe the histopathologic type of the primary tumor. Most of the cases appeared to be either dedifferentiated or high-grade chondrosarcoma. There was 1 well-differentiated case.[20] In that case, the investigator raised the possibility of the tumorigenic potential of a previous Teflon injection.[20]

Management Philosophy. To avoid the underdi-

CHRONOLOGIC REVIEW OF 20 REPORTED CASES OF METASTASIZING LARYNGEAL CHONDROSARCOMA

Author	*Year*	*Age*	*Sex*	*Primary Site*	*Metastasis Site(s)*	*Primary Pathologic Finding*	*Follow-up*
Ungerecht[6]	1951	62	M	Cricoid, trachea	Lungs	NR	NR
Shirota and Hurwitz[7]*	1952	65	M	Cricoid	Lungs, kidney, cervical nodes	"Recurrent" chondrosarcoma	Died 28 mo§
Frenzel[8]	1953	NR	NR	NR	Cervical node	NR	NR
Bronzini[9]	1959	72	M	Corniculate	Cervical node, widespread	NR	Died 18 mo§
Ghalib et al[10]	1969	74	F	Cricoid	Lungs	Grade 2-3† (postirradiation)	Died 3 d§
Al-Saleem et al[11]	1970	71	F	Cricoid	Cervical node	Poorly differentiated (dedifferentiated type†)	Died 12 mo§
Huizenga and Balogh[12]	1970	68	M	Cricoid	Lung, kidney, neck	High grade	Died 13 mo§
Hyams and Rabuzzi[13]	1970	71	F	Cricoid	Thorax, abdomen, subcutaneous node	"Recurrent" chondrosarcoma	Died 30 y§
Hellquist et al[14]	1979	65	F	Cricoid	Lungs, spleen	Highly differentiated with small area of atypia	Died§
Harwood et al[15]	1980	75	M	NR	Lungs	Authors reported "unknown"	Died§
Ferlito et al[2]	1984	74	M	Thyroid	Lungs	Grade 2, dedifferentiated type	Died 30 mo§
Escher et al[16]	1984	NR	NR	NR	Lungs	NR	NR
Gray et al[17]	1984	NR	NR	Epiglottis	Lungs	NR	NR
Kasanzew et al[18]	1988	46	F	Epiglottis	Cervical nodes	Grade 3†	Alive
Jacobs et al[19]	1989	52	M	Epiglottis	Lungs, cervical nodes	Grade 2-3	Alive
Hakky et al[20]	1989	56	M	Cricoid	Cervical nodes	Well-differentiated type (post–Teflon injection)	Alive
Glaubiger et al[21]	1991	57	M	Thyroid†	Cervical nodes, superior mediastinum	Grade 2 (postirradiation)	Alive
Brandwein et al[22]	1992	69	M	Cricoid	Cervical nodes	Dedifferentiated type	Died 17 y
Our case 1		58	F	Cricoid	Cervical nodes	Dedifferentiated type	Died 14 y
Our case 2		62	M	Cricoid	Cervical nodes, clavicle, rib, lung, vertebral body	Dedifferentiated type	Alive

NR — not reported.

*Follow-up reported in Hyams and Rabuzzi.[13]

†Our speculation.

§Tumor-related death.

agnosis of a tumor, biopsy should be carefully and thoroughly conducted. The laryngofissure procedure might be required to obtain an adequate amount of tissue for pathologic evaluation. A specimen should be obtained from each site that has a different gross appearance.

The management of laryngeal chondrosarcoma has been primarily by surgical treatment. Radiotherapy and chemotherapy have generally been ineffective for the treatment of this type of tumor. The selection of the surgical modality should be carefully conducted, depending on the histopathologic type and the resectability of tumor. In general, because of the low level of local aggressiveness, conservative surgery is advisable for grade 1 and most cases of grade 2 chondrosarcoma to preserve laryngeal function. Conservative procedures, however, should be employed only when the tumor can be removed with a sufficient margin.[34] Grade 3 and especially dedifferentiated chondrosarcoma should be treated as separate entities from conventional laryngeal chondrosarcoma because of their proclivity for aggressive behavior.[24,30,31] One should be aware of the high incidence of local recurrence and distant metastasis, especially when treating these tumors by conservative surgery. In our opinion, a more aggressive procedure such as radical resection of the tumor or total laryngectomy is best for this type of tumor. Proper assessment and treatment of this tumor in the larynx can result in over 5 years of survival, as in our case 1 and the patient of Brandwein et al.[22]

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VOICE REHABILITATION AFTER TOTAL LARYNGECTOMY AND TRACHEOESOPHAGEAL PUNCTURE USING NONMUSCLE CLOSURE

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The successful production of voice with a tracheoesophageal puncture (TEP) and voice prosthesis requires a compliant pharyngoesophageal segment. Speech failure is commonly attributed to spasm of the pharyngoesophageal segment. During total laryngectomy (TL), a 3-layer closure is typically performed. This prospective single-arm study examines the safety and efficacy of TL and TEP with nonclosure of the pharyngeal musculature to prevent pharyngoesophageal spasm as an alternative to 3-layer closure with pharyngeal plexus neurectomy and/or pharyngeal constrictor myotomy. Twenty-one consecutive patients were enrolled by a single surgeon. The mean duration of follow-up was 19.5 ± 7.9 months. Surgical complications and voice rehabilitation outcomes were examined. An overall complication rate of 28.5% was observed. Fluency was achieved in 75% of patients within a mean of 4.3 ± 5.1 months. Speech failure was attributable to early primary site and neck recurrence (5%), hypoglossal nerve palsy (5%), hypopharyngeal stricture and recurrence (5%), dementia (5%), and intransigent alcohol abuse (5%). Pharyngeosophageal spasm was not observed in any subjects. We conclude that primary TEP with nonclosure of the pharyngeal muscle during TL is relatively safe. Furthermore, it is preferable over 3-layer closure because it avoids pharyngeosophageal spasm, a factor limiting voice rehabilitation.

KEY WORDS — total laryngectomy, tracheosophageal puncture, voice rehabilitation.

INTRODUCTION

The successful production of voice with a tracheoesophageal puncture (TEP) and duckbill prosthesis requires a compliant pharyngoesophageal segment that produces sound with insufflation. During total laryngectomy (TL), a 3-layer closure is usually performed; the mucosa, submucosa, and pharyngeal constrictor muscles are each closed in a separate layer to create the pharyngoesophagus.[1] Speech failure is commonly attributed to spasm of the pharyngoesophageal segment.[2,3] Pharyngeal plexus neurectomy or pharyngoesophageal myotomy is required to alleviate spasm and to achieve successful voice rehabilitation.[4,5]

Olson and Callaway[6] demonstrated the relative safety of 2-layer, nonmuscle closure during TL in a series of 20 patients from the Veterans Administration Medical Center at the University of Michigan. By not closing the pharyngeal musculature, the 2-layer closure technique tries to eliminate pharyngoesophageal spasm, which prevents the need for secondary procedures such as pharyngeal plexus neurectomy or pharyngoesophageal myotomy.

The present single-arm prospective study examines the safety and efficacy of performing TL with 2-layer, nonmuscle closure and TEP. Patients were enrolled into the present study on a prospective basis and complication rates and speech fluency results are compared with historical controls that employed standard 3-layer closure. We conclude that nonmuscle closure is a relatively safe and effective alternative to the standard 3-layer technique with pharyngeal plexus neurectomy or pharyngoesophageal myotomy.

MATERIALS AND METHODS

Between July 1989 and December 1991, 21 consecutive patients under the care of the senior author (R.M.E.) at the University of Michigan Medical Center were enrolled into the present study on a prospective basis. All patients underwent TL with nonclosure of the pharyngeal musculature. Primary TEP was performed in 19 (90.5%); 2 underwent secondary TEP. Diabetic patients with a history of prior radiotherapy (XRT) felt to be at high risk for wound healing complications were prospectively deemed ineligible for inclusion in this study. Patient characteristics are summarized in Table 1. In accordance with convention, clinical stage at initial presentation is reported in Table 1. Total laryngectomy was performed in 5 patients with apparent early stage disease (stage I or II). All of these patients underwent salvage TL for extensive disease that had failed either induction chemotherapy or primary XRT, or for recurrent disease previously treated with primary XRT that was not amenable either medically or oncologically to a conservation laryngeal procedure.

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TABLE 1. SUMMARY OF PATIENT CHARACTERISTICS

Male	11 (52.4%)
Female	10 (47.6%)
Age (y)	
Mean	60.2
SD	12.6
Range	29-77
Follow-up (mo)	
Mean	19.5
SD	7.9
Median	20.5
Range	10-36
Clinical indication	
Squamous cell carcinoma of larynx	19 (90.5%)
Carcinoma not otherwise specified	2 (9.5%)
Timing of tracheoesophageal puncture	
Primary	19 (90.5%)
Secondary	2 (9.5%)
Clinical stage	
I	1 (4.8%)
II	4 (19.1%)
III	6 (28.5%)
IV	10 (47.6%)
Concomitant surgical therapy	15 (71.5%)
Ipsilateral neck dissection	4 (19.1%)
Bilateral neck dissection	7 (33.3%)
Partial pharyngectomy	4 (19.1%)
Adjuvant therapy	19 (90.5%)
Preoperative radiotherapy	7 (33.3%)
Postoperative radiotherapy	13 (61.9%)
Preoperative chemotherapy	6 (28.5%)
Postoperative chemotherapy	1 (4.8%)

After the tracheostoma was fashioned,[1] primary TEP was accomplished in the midline of the common party wall, 5 to 8 mm from the anticipated superior mucocutaneous junction. Initially securing the entire tracheal ring to the lower skin flap stabilizes the position of the stoma to allow accurate placement of the TEP site when performed primarily. In the 2-layer, nonmuscle closure technique, the first layer (mucosa) is closed with inverting interrupted Connell sutures of 3-0 polyglycolic acid (Dexon, Vicryl). The needle enters the fascia 4 mm lateral to the margin of the mucous membrane and exits in the immediate submucosal layer.[1] A second layer is closed by placing a running suture of 3-0 Vicryl immediately lateral to the initial suture line. This imbricates and buries the first layer. Care is taken not to include elements of pharyngeal constrictor musculature. We have not used a dilator or stent to prevent overclosure of the pharyngoesophageal segment; this has not been a problem, in our experience.

Patients were followed on at least a monthly basis for the first postoperative year and bimonthly thereafter. Successful postoperative tracheoesophageal voice production was based on the patient's ability to produce fluent speech. Parameters for fluent speech production were set in accordance with previously published criteria.[5,7,8] Fluent speech was judged as comparable to that of normal laryngeal speakers, ie, greater than 10 seconds of uninterrupted sound duration and a minimum production of 10 syllables per breath. Further measures of successful tracheoesophageal speech production were indicated by the patient's use of the voice prosthesis with sufficient strength and clarity for all communication needs. Patients also independently managed their voice prostheses with minimal follow-up by the speech pathologist.

RESULTS

An overall complication rate from TL with 2-layer, nonmuscle closure and TEP of 28.5% was noted. Three patients (14.3%) developed stomal stenosis. The tracheostoma was considered stenotic if the patient had to wear a laryngectomy tube permanently or required a stomaplasty procedure. Two became fluent with a Blom-Singer prosthesis within 2 months of stomal revision. Two of the 3 patients who developed stomal stenosis received postoperative XRT. None received chemotherapy.

Two patients (9.5%) developed postoperative pharyngocutaneous salivary fistulae. Salivary leakage was noted in the immediate postoperative period and healed by conservative treatment with pressure dressings and antibiotics in both cases. Each subsequently tolerated 6,000 cGy XRT without associated complications. No pharyngocutaneous salivary fistulae developed in the 7 patients who underwent surgical salvage after irradiation failure.

One patient developed a stomal stitch abscess that responded to removal of the stitch during a clinic visit followed by a brief course of oral antibiotics and dressing changes.

Fifteen (75.0%) of 20 patients available for follow-up achieved fluent voice restoration. One patient unavailable for follow-up died 7 weeks postoperatively as a result of caustic ingestion. The mean duration until development of fluency was 4.3 ± 5.1 months (median 3.5, range <1 to 19). The patients who did not receive either preoperative or postoperative XRT developed fluency within 1.67 ± 0.3 months; all of these patients became fluent. In contrast, 63.6% of the 13 patients undergoing postoperative XRT developed fluency within 6.1 ± 5.3 months. Of the 7 patients with surgical salvage after XRT, 83.3% developed fluency within 2.6 ± 0.8 months. Therefore, speech acquisition was significantly delayed in the patients receiving postoperative XRT. Pharyngoesophageal spasm was not observed in any subjects

TABLE 2. OPERATIVE COMPLICATIONS IN PRESENT SERIES COMPARED TO SERIES WITH 3-LAYER CLOSURE

Complications	*Authors*	*Year*	*Operations Reported*	*%*
Overall	**Present series**	**1992**		**28**
	Ho et al[9]	1991	Primary TEP	42
	Maniglia et al[10]	1989	Primary TEP	36
	Maniglia et al[10]	1989	Secondary TEP	23
	Andrews et al[11]	1987	Combined	25
	Silver et al[8]	1985	Secondary TEP	15
Stomal stenosis	**Present series**	**1992**		**14**
	Ho et al[9]	1991	Primary TEP	19
	Trudeau et al[12]	1989	Primary TEP	22
	Trudeau et al[12]	1989	Secondary TEP	29
	Yonkers and Mercurio[13]	1983	TL	42
	Lam et al[14]	1983	TL	31
	Griffith and Luce[15]	1982	TL	22
	Langenbrunner and Chandler[16]	1968	TL	34
Pharyngocutaneous fistula	**Present series**	**1992**		**9**
	Ho et al[9]	1991	Primary TEP	18
	Singer et al[17]	1989	Primary TEP	24
	Maniglia et al[10]	1989	Primary TEP	24
	Maniglia et al[10]	1989	Secondary TEP	18
	Andrews et al[11]	1987	Combined	10

TEP — tracheoesophageal puncture, Combined — combined experience with primary and secondary TEP, TL — total laryngectomy.

TABLE 3. VOICE RESTORATION IN PRESENT SERIES COMPARED TO SERIES WITH 3-LAYER CLOSURE

Tracheoesophageal Puncture	*Authors*	*Year*	*% Pts With Voice Restoration*
Primary	**Present series**	**1992**	**75**
	Juarbe[18]*	1989	81
	Maniglia et al[10]	1989	88
	Shagets and Panje[19]	1985	74
	Hamaker et al[20]	1985	75
	Maves and Lingeman[21]	1982	82
Secondary	Juarbe[18]†	1989	83
	Maniglia et al[10]	1989	69
	Amatsu et al[22]	1985	81
	Panje (cited in Juarbe[18])	1983	83
	Johns and Cantrell[23]	1981	92
	Singer et al[3]	1981	88

*Meta-analysis of 300 patients undergoing primary tracheosophageal puncture, from 9 reports published 1982 to 1989. Range 58% to 97%. Mean 81%.

†Meta-analysis of 700 patients undergoing secondary tracheoesophageal puncture, from 11 reports published 1981 to 1989. Range 57% to 93%. Mean 83%.

on clinical evaluation, videofluoroscopy, or esophageal insufflation testing.[7]

DISCUSSION

This study demonstrates that TEP with 2-layer, nonmuscle closure during TL is relatively safe and that it is not associated with a higher operative complication rate than would be expected with standard 3-layer closure accompanied by either primary or secondary TEP (Table 2[8-17]). We present a rate of fluency that compares favorably with both primary TEP and secondary TEP in TL with standard 3-layer closure (Table 3[3,10,18-23]). Although patients were entered into the present study on a prospective basis, our results are compared with historical controls drawn from the literature. We recognize the bias associated with the heterogeneity of patients, treatments, and surgical technique with the use of historical controls, and we have reviewed the literature in detail. Our results are presented in Tables 2 and 3 so that the reader may compare our findings in the context of the range of reported results.

Tracheoesophageal puncture has been associated with significant operative morbidity in 15% to 43% of cases. Reported major complications related to TEP include mediastinitis, cervical cellulitis, sepsis, esophageal perforation, deep neck abscess, and fracture of the cervical spine.[9,11,24,25] These are complications related to TEP and not to the pharyngeal closure per se. We demonstrated that TEP may be performed relatively safely with 2-layer, nonmuscle closure. The overall major and minor operative complication rate in the present series with TEP and 2-layer closure is 28.5%; this falls within an acceptable range in comparison with reports in the literature (Table 2).

The development of postoperative pharyngocutaneous fistula is a common complication of TL; it delays recovery and oral intake, alters the expeditious scheduling of XRT, prevents voice rehabilitation, and promotes stricture formation. We observed 2 (9.5%) cases of postoperative salivary fistulae. When combined with the series of 20 patients that were contributed by the senior author to the study of Olson and Callaway,[6] the overall fistula rate with nonmuscle closure in a single surgeon's experience is 10% (4 of 41 patients). Review of the literature on pharyngocutaneous fistula formation following TL and TEP reveals an expected rate of 10% to 25%[12,19,24,25] (Table 2).

We observed 3 (14.3%) cases of stomal stenosis. Two of these patients underwent postoperative XRT; another case was complicated by a previous median sternotomy, sternal wound infection, and manubrium resection. The reported incidence of tracheostomal stenosis in most series ranges from 22% to 42%.[13-17,25] Our rate of stomal stenosis with TEP and 2-layer closure compares favorably with these rates

(Table 2).

Pharyngoesophageal spasm is manifested clinically by a sudden increase in pitch and pressure with an abrupt termination of produced sound. Singer and Blom[4] attributed failure to achieve satisfactory speech after TEP to pharyngoesophageal spasm in 12% of patients. On a prospective basis, pharyngoesophageal spasm was noted in 28% to 55% of patients.[2,20] Despite intensive speech therapy prior to pharyngeal myotomy, no patient with pharyngoesophageal spasm developed volitional control over tracheoesophageal speech without operative intervention.[4,5] Near-complete acquisition of tracheoesophageal voice was reported in patients with disabling spasm who underwent selective myotomy.[4,5] Hamaker et al[20] suggested myotomy of the pharyngeal constrictors at the time of TL in all patients.

Reported operative complications of myotomy include wound infection, sepsis, gastroesophageal reflux, postoperative hematoma, inadequate myotomy, inadvertent pharyngotomy with salivary fistula formation, stomal stenosis, an adynamic pharyngoesophageal segment, residual spasm, and need for reoperation.[4,5] The procedure may be associated with a flaccid pharyngoesophageal segment and a deep, breathy, unacceptable voice.[5]

The virtue of nonmuscle closure in TL with TEP is that it avoids pharyngoesophageal spasm and therefore obviates the need for myotomy and/or neurectomy and their attendant complications. However, with the relative safety of 2-layer closure having been demonstrated, these results must be considered within the context of restoration of a fluent alaryngeal voice. Juarbe[18] reviewed 11 reports of secondary TEP from 1981 to 1989, encompassing over 700 patients, that revealed a success rate of 57% to 93%. The nearly 300 patients included in 9 series of primary TEP reported from 1982 to 1989 revealed a fluency rate ranging from 58% to 97%.[11] We observed a speech fluency rate of 75%, which compares favorably with those reported in 3-layer closure (Table 3). None of the cases in the present series required pharyngeal plexus neurectomy or pharyngeal myotomy with their risks or attendant complications.

A wide variation in speech acquisition was observed. Three patients who experienced complicated and protracted postoperative courses may be considered outliers. In uncomplicated cases (12 of 15), fluency was achieved in 2.0 ± 0.3 months. In the 3 complicated outlier cases, speech was eventually acquired in 7 to 19 months. Each of the 3 complicated cases were in patients with postoperative XRT. The cases were complicated by recurrent neck disease treated by postoperative hyperfractionated XRT and chemotherapy; by esophageal stricture secondary to recurrent disease treated by completion pharyngectomy, jejunal microvascular reconstruction, and XRT; and by marked stomal stenosis requiring stomaplasty in the setting of postoperative XRT. Although the numbers are small, there is a trend toward improved fluency rates in patients who did not receive XRT. Five patients (25%) failed to achieve voice restoration. None failed because of pharyngoesophageal spasm. One patient failed because of dementia, and another secondary to intransigent alcohol abuse with resultant poor compliance with planned speech rehabilitation. One patient developed hypopharyngeal stenosis requiring dilation and eventual reconstruction with a pectoralis myocutaneous flap precluding voice rehabilitation. Another patient with a third recurrence after XRT and TL underwent salvage pharyngectomy, chemotherapy, and XRT boost to 7,000 cGy. This patient developed recurrent aspiration and died with disease 14 months after TL. The final speech failure was attributable to hypoglossal nerve paralysis. The hypoglossal nerve was extensively mobilized and preserved during salvage surgery after chemotherapy and XRT, yet tongue paralysis resulted.

We conclude that TEP with 2-layer closure during TL is relatively safe. This modification of the standard surgical technique that leaves open the pharyngeal constrictor musculature is not associated with a higher operative complication rate than would be expected in standard 3-layer closure accompanied by either primary or secondary TEP. Pharyngoesophageal spasm, a problem limiting voice restoration in 3-layer closure, was not observed in the present investigation. Total laryngectomy with nonmuscle closure avoids the need for secondary procedures such as pharyngeal constrictor myotomy or pharyngeal plexus neurectomy and their attendant complications.

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SAN FRANCISCO OTOLOGY, NEUROTOLOGY, & SKULL BASE SURGERY UPDATE — 1993

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POSITRON EMISSION TOMOGRAPHY OF AUDITORY SENSATION IN DEAF PATIENTS AND PATIENTS WITH COCHLEAR IMPLANTS

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The present study investigated the function of the auditory cortices in severely hearing-impaired or deaf patients and cochlear implant patients before and after auditory stimulation. Positron emission computed tomography (PET), which can detect brain activity by providing quantitative measurements of the metabolic rates of oxygen and glucose, was used. In patients with residual hearing, the activity of the auditory cortex measured by PET was almost normal. Among the totally deaf patients, the longer the duration of deafness, the lower the brain activity in the auditory cortex measured by PET. Patients who had been deaf for a long period showed remarkably reduced metabolic rates in the auditory cortices. However, following implantation of the cochlear device, the metabolic activity returned to near-normal levels. These findings suggest that activation of the speech comprehension mechanism of the higher brain system can be initiated by sound signals from the implant devices.

KEY WORDS — auditory cortex, cochlear implant, deafness, positron emission computed tomography, speech comprehension.

INTRODUCTION

Over the last 2 decades a number of medical centers have attempted to perform cochlear implant surgery for deaf patients.[1] The multichannel cochlear implant is currently widely used; however, the electrode signals to the brain are very simple compared to those from the normal cochlea. Even so, patients with cochlear implants show improved speech comprehension ability. Several months after cochlear implantation, the patients are able to understand everyday conversation without lipreading.[2] Higher brain activities are thought to contribute to this improvement.

Brain activities have been investigated in animal experiments, although few successful experiments[3] have been reported. The relationship between human brain activities and audition is still not well understood. Positron emission computed tomography (PET) has recently been used for physiologic and biochemical measurements in specific brain regions.[4] It provides quantitative measurements of regional metabolic rates for oxygen and glucose in humans. A 3-dimensional representation of the brain, with resolution better than 2 cm in both the horizontal and vertical planes, can be constructed with PET. In the auditory cortex area, PET was used to map alterations in local neuronal activity and systematic changes in activity that depend on the frequency of the stimulating pure tone.[5]

The purpose of the present study was to investigate the metabolic function of the auditory cortex in severely hearing-impaired or deaf patients by means of PET. In some cochlear implant patients, we compared PET before and after the cochlear implant operation. Our results show that PET can be used to assess functional changes of the auditory cortex.

MATERIALS AND METHODS

A whole-body, multislice positron emission com-

CLINICAL CHARACTERISTICS OF PATIENTS ON WHOM PET WAS PERFORMED

	Pt No.	*Age*	*Sex*	*Cause of Deafness*	*Duration of Deafness (y)*
Hearing impairment	1*	26	F	Otosclerosis	5
	2	41	M	Sudden deafness	3
Deafness of short duration	3*	42	M	Head injury	1
	4†	51	M	Meningitis	1
	5	53	M	Meningitis	2
	6*	54	F	Meniere's disease	3
	7*	58	F	Sudden deafness	5
	8	52	F	Unknown	5
Deafnesss of long duration	9†	59	M	Meniere's disease	10
	10	61	M	Streptomycin	25
	11†	38	M	Streptomycin	37

PET — positron emission computed tomography.
*With cochlear implantation and preoperative PET.
†With cochlear implantation and both preoperative and postoperative PET.

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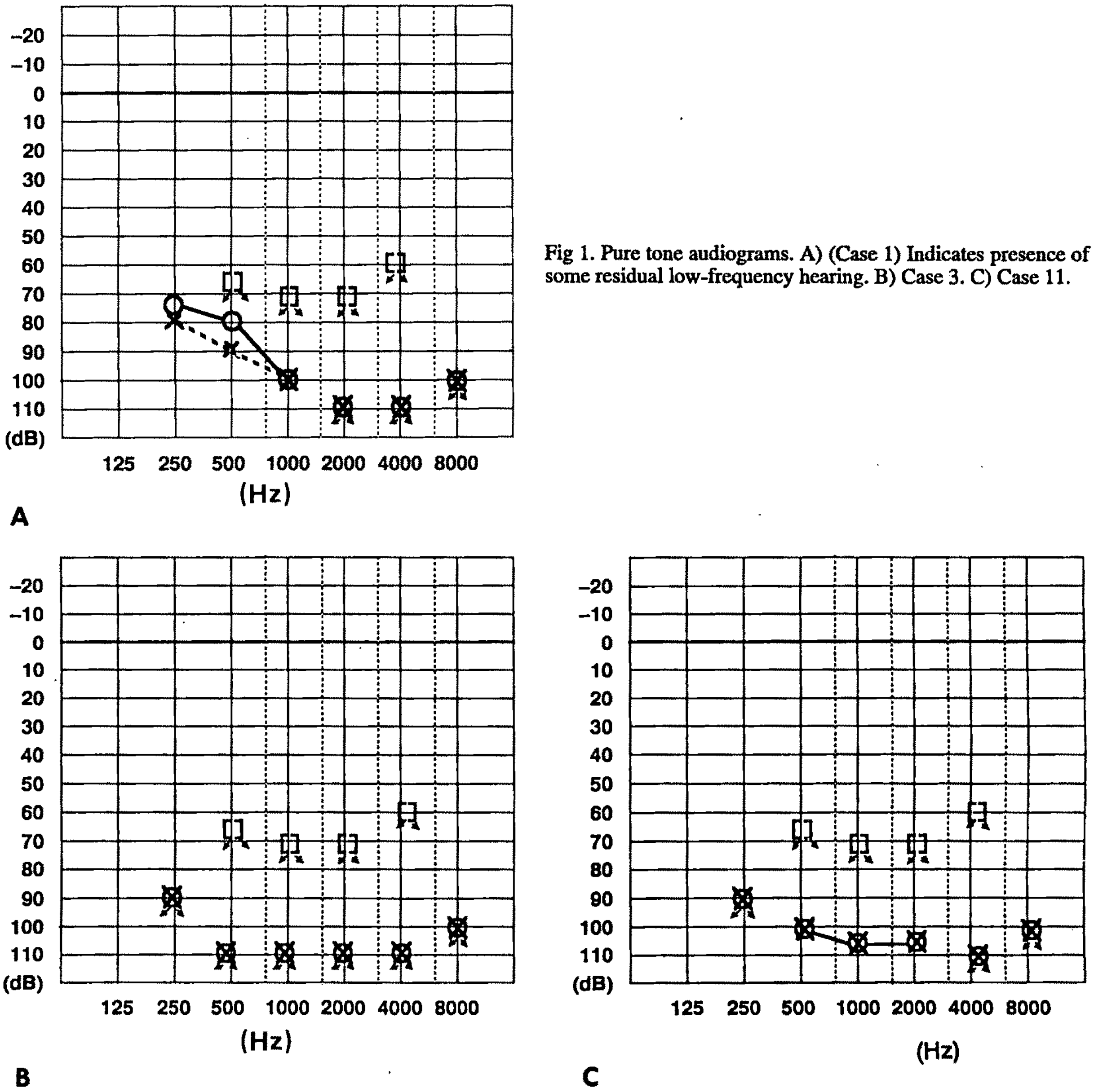

Fig 1. Pure tone audiograms. A) (Case 1) Indicates presence of some residual low-frequency hearing. B) Case 3. C) Case 11.

puted tomograph, Positologica III, was used in this study. A positron-releasing chemical, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), was used to measure local changes in cerebral glucose metabolism. A detailed explanation of the PET scanning procedure has been reported elsewhere.[6]

The Table shows the clinical characteristics of the patients on whom PET was performed. The patients were divided into 2 groups depending on whether they were severely hearing-impaired (cases 1 and 2) or totally deaf (cases 3 through 11). In addition, the totally deaf patients were divided into 2 groups: those who had been deaf for a relatively short period of time (cases 3 through 8) and those who had been deaf for a long period of time (cases 9 through 11). Seven patients underwent cochlear implant surgery. Three of these patients underwent PET both before and after surgery. Postoperative PET was performed during auditory stimulation.

PROFOUND HEARING IMPAIRMENT

Case 1. This patient, a 26-year-old woman, first noticed hearing impairment at the age of 12, after which the disturbance became progressively worse. By the age of about 22 she could no longer hear, even with the use of a high-powered hearing aid. At the age of 26, she underwent a cochlear implant operation. Figure 1A show her preoperative audiogram.

TOTAL DEAFNESS OF SHORT DURATION

Case 3. This patient, a 42-year-old man, had fallen from a height of 5 m and been found to have a

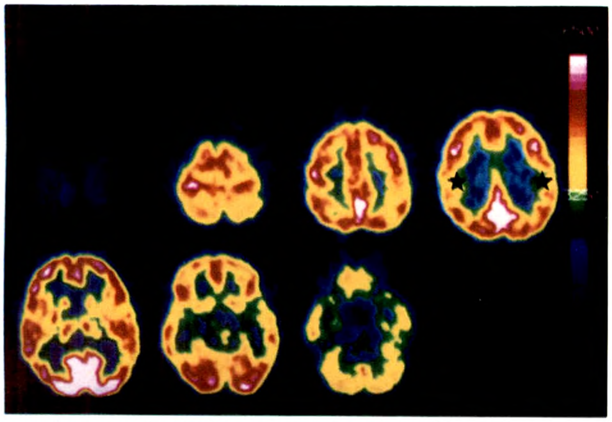

Fig 2. Positron emission computed tomography (PET) images of normal-hearing volunteer. Stars show bilateral transverse temporal gyri (Heschl), where primary auditory cortices are located. In all PET images, different colors indicate different rates of glucose metabolism. That is, red is high rate, yellow is moderate, and blue is low, as shown on right vertical bar.

temporal bone fracture by high-resolution computed tomography. He became totally deaf 1 year before cochlear implantation. Figure 1B shows his preoperative audiogram.

Case 4. A 51-year-old man became totally deaf from meningitis 1 year before cochlear implantation. In this case, we performed PET both before and after cochlear implantation. The postoperative PET scan was taken after the patient had been told to listen carefully to sound stimulation.

TOTAL, PROFOUND DEAFNESS OF LONG DURATION

Case 10. A 61-year-old man had been given streptomycin at the age of 32 for pulmonary tuberculosis and became totally deaf 3 or 4 years later.

Case 11. This patient, a 38-year-old man, had been given streptomycin for pulmonary tuberculosis at the age of 1 year and became almost deaf several months later. This patient is a so-called prelingually deaf patient. The preoperative audiogram (Fig 1C) shows that while the patient did have some residual hearing, he could hardly understand speech even with the aid of a high-powered hearing aid. He underwent cochlear implantation, and we compared the PET images before and after operation.

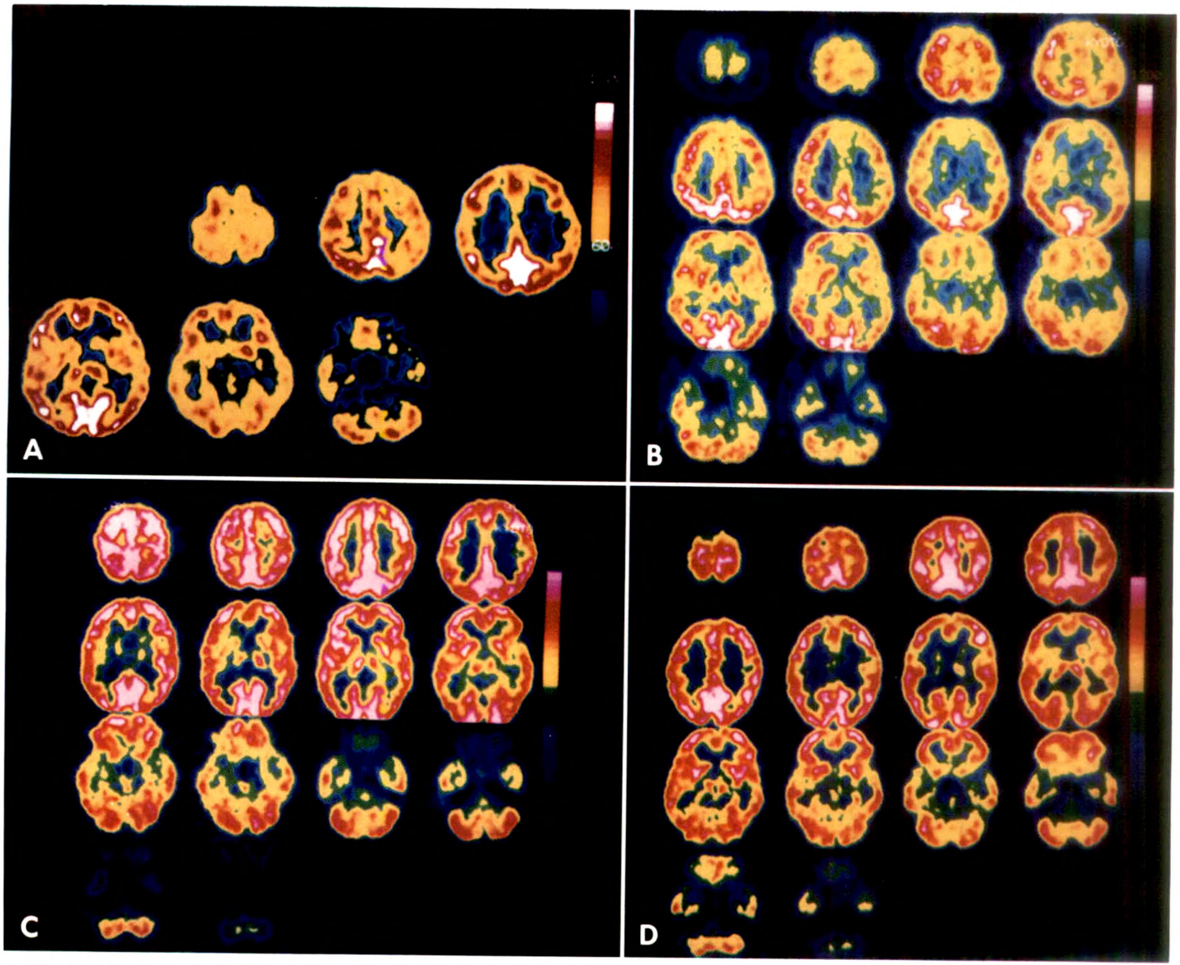

Fig 3. PET images. A) Case 1. B) Case 3. C) Case 4 before cochlear implantation. D) Case 4 after cochlear implantation. Color bars as in Fig 2.

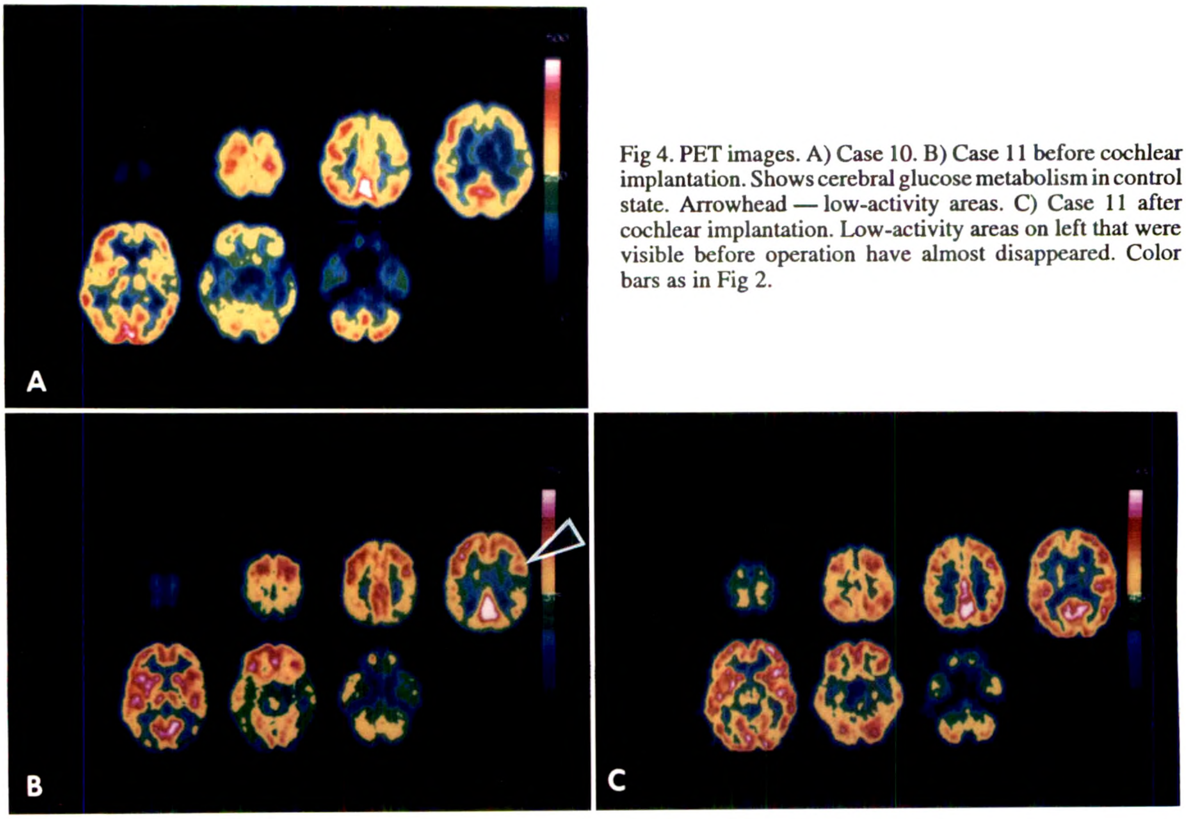

Fig 4. PET images. A) Case 10. B) Case 11 before cochlear implantation. Shows cerebral glucose metabolism in control state. Arrowhead — low-activity areas. C) Case 11 after cochlear implantation. Low-activity areas on left that were visible before operation have almost disappeared. Color bars as in Fig 2.

RESULTS

NORMAL HEARING

Figure 2 shows the PET image of a normal-hearing volunteer.

PROFOUND HEARING IMPAIRMENT

Figure 3A shows the PET images of the case 1 patient. The PET images of this patient appear to be almost normal, even though the audiogram does not reveal a good response to sound. The PET images of another patient (case 2) with residual hearing were also almost normal.

TOTAL DEAFNESS OF SHORT DURATION

Figure 3B shows the PET images of the auditory cortex of the case 3 patient. There was a slight decrease in the metabolic rate for the primary auditory cortices bilaterally, but as such changes can be observed in persons with normal hearing, this PET image could be considered normal. In case 4, we performed PET both before and after cochlear implantation. Figure 3C shows the PET images before operation. There is a slight decrease in metabolic rate of the primary auditory cortex bilaterally. The postoperative PET was taken after the patient had been told to listen carefully to sound stimulation. As Fig 3D shows, the postoperative PET images of this patient appear almost normal.

TOTAL DEAFNESS OF LONG DURATION

Figure 4A shows the PET images of the case 10 patient. There are remarkable metabolic decreases, especially in the left frontal lobe and bilateral temporal lobes. Around the Heschl gyrus, where the primary auditory cortex is located, the metabolic rate was found to be remarkably low.

Figure 4B shows the preoperative PET images of the case 11 patient. There is a remarkably low metabolic rate in the primary auditory cortex and in some of the associated cortex preoperatively. The postoperative PET was obtained during auditory stimulation. In this case, as well, the patient had been instructed to listen carefully to the sound stimulation. As Fig 4C shows, the metabolic rate in the primary and secondary auditory cortices returned to near-normal levels.

DISCUSSION

Several months to years of rehabilitation are generally considered necessary for patients with cochlear implants to recover their speech perception ability. However, in our experience, the ability to discriminate vowels and consonants and the ability to discriminate speech tracking reaches a plateau 3 to 4 months after the operation.[2] Even though the signals generated by the implanted electrodes are very simple compared to those from the normal cochlea, the patients develop significant speech comprehension. Perhaps the higher brain system contributes to this improvement.

Our findings demonstrate that the PET measurements of patients with residual hearing are almost normal, and that the metabolic rate in the auditory cortex in patients who have been deaf for a short period of time is nearly normal or slightly decreased.

On the other hand, patients who have been deaf for a long time show decreased activity in the auditory cortex. We can conclude that if the period of deafness is long, eg, over 10 years, the primary auditory cortex, as well as the secondary associated cortex, will exhibit a low metabolic rate.

Speech discrimination rehabilitation in prelingually deafened patients, as in case 11, has been reported to be more difficult than in postlingually deafened patients.[7] In this case, the score on the vowel confusion study was still only 40% 1 year after the operation. Preoperative PET on this subject showed large low-activity areas throughout the primary auditory cortex and associated cortex, which may be caused by the absence of sound signal inputs. However, after beginning rehabilitation, the PET images during sound stimulation showed increased levels of activity in the left parietal cortex. It is interesting to note that this increase was found not only in the primary auditory cortex, but also in the auditory-associated cortex. These PET findings suggest that the speech comprehension mechanism of the higher central nervous system can be activated by simple sound signals from the cochlear implant device, and also suggest that the patient's hearing will improve during the course of future rehabilitation.

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EARLY-STAGE DEVELOPMENT OF AUDITORY CENTER: AN EXPERIMENTAL STUDY OF AUDITORY EVOKED ELECTROPHYSIOLOGIC RECORDINGS FROM FETAL AND NEWBORN GUINEA PIGS

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Five guinea pig fetuses at 8 weeks' gestation (term is 9 weeks) were tested for auditory brain stem response (ABR) generated by earphones placed outside the maternal abdomen. The results obtained from these fetuses were compared with the ABRs in 10 term newborn guinea pigs on the 1st and 20th days after delivery. The ABRs indicated a decreasing peak latency over wave III with increasing age. The interpeak latency to wave III-V decreased markedly, with very little change in wave I-III. The results suggested rapid maturation of the upper brain stem and midbrain during late gestation and in newborns. They also exhibited an increasing peak latency of ABRs from both fetuses and newborns with decreasing stimulus intensity.

KEY WORDS — auditory brain stem response, fetus, guinea pig, newborn.

INTRODUCTION

Changes in fetal movement and heart rate have been observed in response to external auditory stimulation, ie, sound from a speaker placed on the maternal abdomen. There is little or no information, however, in humans or in animals, regarding the electroneurologic auditory brain stem response (ABR) to external sound in fetuses.[1] Understanding of the causes of congenital hearing loss is handicapped by our limited knowledge of the ABR from fetuses and the process of early development in the auditory pathway. The ABR is a neuroelectrical response from the brain stem auditory pathway to a series of click stimulations, detected by computer signal-averaging techniques. It has been used successfully to confirm hearing acuity in human adults and infants. Recently, it has been reported that serial measurement of ABR from fetal lambs may be an appropriate method for the assessment of hearing development in utero.[2]

The purposes of the present study were to verify the possibility of recording ABRs from fetal guinea pigs in utero at a late gestational age and to compare these with the ABRs obtained from newborn guinea pigs at 2 different periods following delivery. The maturational characteristics of early development in the auditory center are defined.

MATERIALS AND METHODS

Five fetal guinea pigs in different mothers were used to measure fetal ABRs at 8 weeks' gestation. (Term is about 9 weeks.) The mothers were given 2% sodium pentobarbital intramuscularly and then 1% procaine as a local anesthetic. Midline abdominal incisions were made to expose the uterus, and the fetal head was exposed through a uterine incision. A stainless steel electrode with a hooked anterior end was inserted subdermally at the vertex to serve as the active electrode. Except for its tip, the needle was covered with insulating paint and encased in silicone tubing. A second, similar electrode was placed anterior to the pinna as a reference electrode. After fetal instrumentation was completed, we returned the fetal head to the uterus and pulled the electrode leads through the abdominal incision to the outside. We closed the incision and placed the earphone close to the abdomen. The fetal ABRs were measured immediately. All fetuses survived with normal heartbeats until 24 to 48 hours after the measurement and then were delivered prematurely.

In addition, 10 term newborn guinea pigs, spontaneously delivered, were submitted to bilateral ABR testing with needles placed subdermally in the same position as in the fetal animals. In addition, a ground electrode was placed in the nose. The earphones were placed outside the external ear canal, as close as possible to the ear. The newborns were tested twice, on the 1st and 20th days after delivery.

The ABR was obtained with the Madsen 2250

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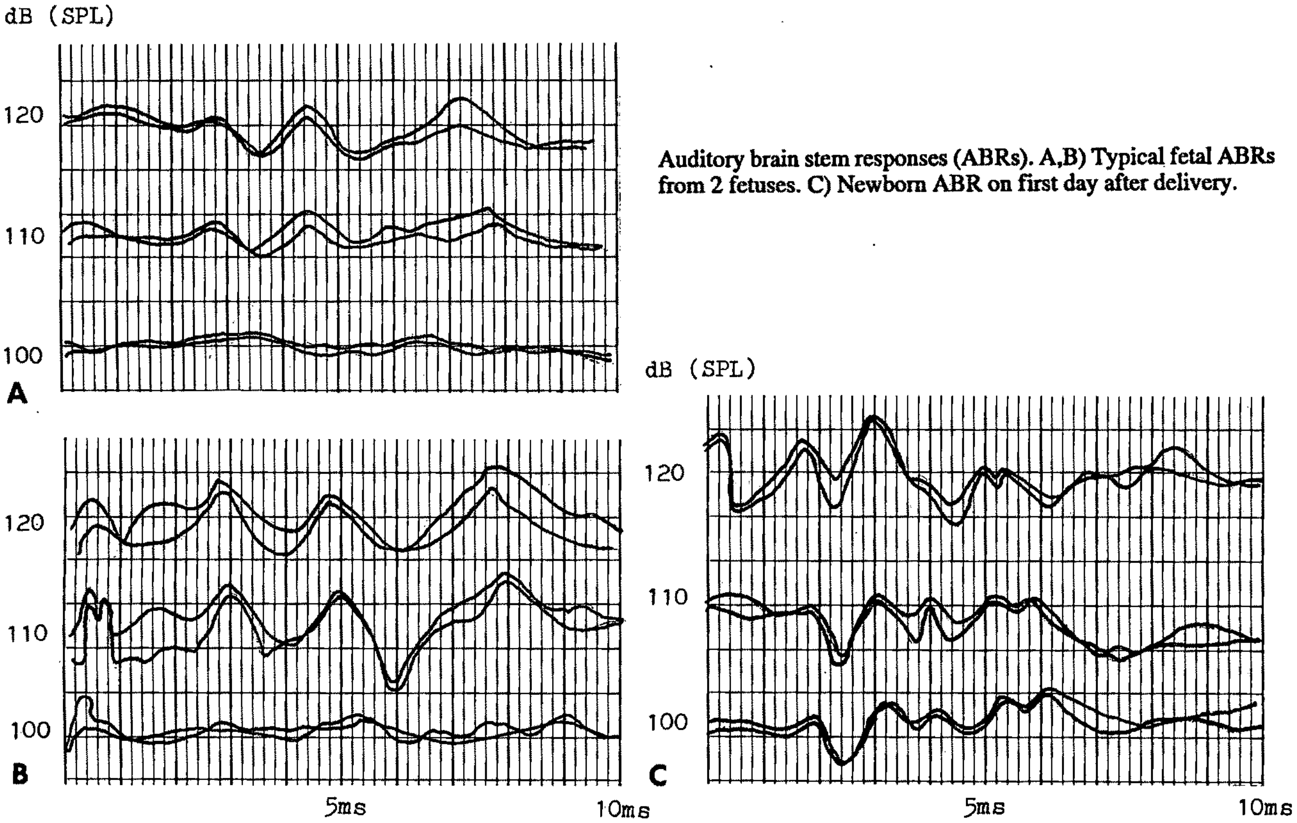

Auditory brain stem responses (ABRs). A,B) Typical fetal ABRs from 2 fetuses. C) Newborn ABR on first day after delivery.

electronic response auditory instrument (Madsen Co, Oakville, Canada). Each click represented a square wave of 0.125 millisecond's duration, and they were of alternating pulse polarities. A 200-click stimulus was presented at a rate of 20 clicks per second and was amplified 10^6 times, with a 200- to 2,500-Hz band pass and a 50-microsecond point-sampling interval. The stimulus intensity started at 120 dB sound pressure level (SPL) and decreased progressively in 10-dB steps. We recorded only those wave deflections that were reproducible, ie, when the latency varied by no more than 0.2 millisecond from the previous ABR recording.

RESULTS

In all 5 fetuses, reproducible deflections of ABR were recorded clearly at stimulus intensities of 120 dB and 110 dB. The ABR consisted of 3 reproducible waves — waves I, III, and V — with waves II and IV unclear. When the stimulus was decreased to 100 dB, the reproducible deflections disappeared. Two typical ABRs from fetuses are shown in the Figure (A,B). The ABRs from the 10 term newborns consisted of 4 or 5 waves (see Figure, C). The mean ABR latencies in all fetuses and newborns are presented in the Table. As compared with fetal ABRs, the interpeak latencies from the newborns decreased. Specifically, interpeak latencies to wave III-V from newborns on the 20th day changed markedly ($p < .001$), and the change in wave I-V was also obvious ($p < .001$), with little decrease in wave I-III ($p > .05$). The peak latencies from both fetuses and newborns increased with decreasing stimulus intensity (see Figure).

DISCUSSION

Guinea pigs were chosen partly because they are a model much used previously in auditory electroneurologic research. Thus, the present results can be related to a wealth of existing information. Also, guinea pigs are obtained more easily and economically than fetal lambs.

Apparently, stimulus intensities over 100 dB SPL must be used to elicit an ABR in utero. This result was similar to that of Plessinger and Woods.[3] Perhaps the skin, abdominal wall, and amniotic fluid decrease the sound intensity from the external speaker to the fetus.

The typical fetal ABR consists of only 3 waves — I, III, and V — rather than the 4 or 5 waves of newborns. The reasons for this finding are unclear, but it is similar to that in humans, in whom waves II and IV cannot be recognized clearly until 72 hours after birth.[4]

Comparison of ABRs from fetal guinea pigs with those from newborn ones at 2 different ages shows a steady decrease in almost all ABR latencies with

PEAK AND INTERPEAK LATENCIES OF AUDITORY BRAIN STEM RESPONSE

Group	*Wave I*	*Wave III*	*Wave V*	*Wave I-III*	*Wave III-V*	*Wave I-V*
Fetus (n = 5)	2.76 ± 0.10	4.53 ± 0.27	7.52 ± 0.31	1.77 ± 0.18	2.99 ± 0.33	4.75 ± 0.26
Newborn (1st day; n = 10)	1.72 ± 0.29	3.65 ± 0.31	6.16 ± 0.30	1.90 ± 0.28	2.52 ± 0.40	4.47 ± 0.36
Newborn (20th day; n = 10)	1.72 ± 0.22	3.57 ± 0.15	5.58 ± 0.34	1.88 ± 0.28	1.94 ± 0.33	3.82 ± 0.37

Data are mean ± SD in milliseconds. Stimulus was 110 dB sound pressure level.

advancing age. It is difficult, however, to compare the latencies in all 5 waves between fetuses and newborns, because waves II and IV from fetuses cannot be measured easily. Therefore, the peak latencies to waves I-III, III-V, and I-V are compared between different stages of development. In previous research reported by Plessinger and Woods,[3] a comparison in fetal lambs of the latencies to all waves, especially to wave I, obtained from external auditory stimulation with those from intrauterine stimulation indicates an obvious response delay to external sound. This observed delay of the peak latencies may be caused by the maternal abdominal wall and uterus, delaying the external sound. As a result, the fetal ABR latencies are longer in externally elicited ABRs. However, despite the delay in the peak latencies, similar central conduction times of all interpeak latencies from external and intrauterine stimulation indicate that there is no significant delay in brain stem or midbrain transmission, once the auditory signals from the peripheral auditory apparatus enter the brain stem. In this study, therefore, the differences in interpeak latencies with increasing age were considered important.

In comparison to those of a fetus, the latencies to waves III and V in newborns decrease more markedly than those to wave I. The interpeak latencies to waves III-V and I-V continue to change markedly with increasing age. These data suggest that the peripheral auditory structure matures earlier and undergoes little change in late gestation or after birth, while the higher regions of the brain stem mature more rapidly during the same time. The feature of change is similar to early auditory development in humans and lambs.[5,6] In the preterm human newborn, ABR has not been identified until 26 to 28 weeks' gestation. Then, changes of ABR are reflected as changes primarily in the auditory nerve and cochlear nuclei (waves I and II). After 34 weeks' gestation, the human newborns reflect little change in wave I or II, while maturation continues in the upper regions of the brain stem and midbrain (waves III, IV, and V). It is emphasized that interpeak latency to wave III-V decreases markedly with increasing age and can be used in research of auditory development at an early stage as an aid in identification of the individual wave components.

Interpeak latencies to wave I-V from newborns are much shorter than those from fetuses. Obviously, the difference is due to the effects of latency in wave III-V rather than to those in wave I-III.

In both fetuses and newborns, all of the peak latencies decreased with increasing stimulus intensity. Our current results confirm those previously published for fetal and newborn lambs.[5]

A more precise definition of an earlier stage of auditory development is essential if we want to understand the causes of congenital sensorineural hearing loss. From a fetus at a late gestational age to newborns at 2 different periods after delivery, remarkable changes occur in the upper region of the central auditory system. According to Saunders,[7] this period of rapid change may be dangerous for the central auditory system. Any exposure to ototoxic perinatal events during this period may greatly increase the risk of permanent auditory damage.

To our knowledge, the intrauterine fetal ABR in guinea pigs is measured successfully here for the first time. The model presented in this study offers an easy and reliable opportunity to research a variety of problems regarding fetal auditory development.

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GROWTH RATE OF ACOUSTIC NEUROMA EXPRESSED BY KI-67 NUCLEAR ANTIGEN VERSUS SYMPTOM DURATION

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The growth rate of acoustic tumors varies widely. An immunohistochemical study with Ki-67 monoclonal antibody was performed on a random sample of 21 acoustic neuromas. The tumors belonged to 2 well-defined groups: 1 with a short duration of preoperative symptoms (<1 year) and 1 with a long duration of preoperative symptoms (>5 years). The tumors were of small to medium size (7 to 27 mm), and no large, cystic, or Recklinghausen tumors were included. The tumor proliferative fraction expressed by monoclonal antibody Ki-67 was determined. The results revealed a significant relation between the tumor proliferative fraction and symptom duration. Tumors with a high proliferative status had a short preoperative symptom duration, while tumors with a low proliferative status had a long symptom duration. The clinical implications of these results are discussed.

KEY WORDS — acoustic neuroma, monoclonal antibody, symptom duration, tumor proliferative fraction.

Acoustic neuroma is the most common neoplasm in the cerebellopontine angle.[1] During the past decade the neuropathologic analysis of acoustic tumors has been markedly affected by the application of special techniques for studying tumor histogenesis and growth. Particularly with respect to growth factors, cytogenetics, and cell cycle kinetics, improvements in histopathologic criteria with immunohistochemical and molecular techniques will continue to change the diagnostic tableau.

Several methods have been used to determine tumor proliferative fraction (TPF) in vitro; however, a reliable and practical method for clinical application is not available yet.[2]

Mitotic count has been applied by pathologists as a prognostic criterion in malignant tumors, but the method may not be reproducible, as fixation of sections can affect the number of mitoses.[3,4] Moreover, the mitotic phase reflects only a small part of the proliferation cycle. The cells that are actively synthesizing DNA can be labeled, for example by radioactive thymidine. The TPF determined by this method has been shown to correlate with clinical behavior in certain malignancies.[5,6] However, this method is difficult and time-consuming.

In 1984, DNA flow cytometry was applied on acoustic neuromas by Rasmussen et al,[7] who used flow cytometric DNA analysis to quantify the proportion of cells in the S phase of the cell cycle, but they did not find any correlation with duration of symptoms, age of the patient, or size of the tumor, although the highest S phase percentage was found in the only recurrence tested.

Recently, immunohistochemical methods demon-

TABLE 1. AGE, SEX, TUMOR SIZE, AND KI-67 COUNTS IN TWO GROUPS OF PATIENTS WITH ACOUSTIC NEUROMA

Pt No.	*Age (y)*	*Sex*	*Tumor Size (mm)*	*Count*
Symptom duration <1 year				
1	52	M	27	13.1
2	69	F	8	21.7
3	61	F	8	8.7
4	55	F	15	7.2
5	67	M	10	18.5
6	51	F	25	15.0
7	62	F	15	15.1
8	53	F	8	4.9
9	62	F	30	7.3
10	56	F	12	11.9
11	54	M	10	8.0
Symptom duration >5 years				
12	65	M	12	9.2
13	64	M	15	1.0
14	43	M	7	1.2
15	65	F	10	2.4
16	69	F	15	4.9
17	52	M	20	3.8
18	36	M	20	7.3
19	61	M	10	9.4
20	71	M	15	6.0
21	64	F	7	36.3

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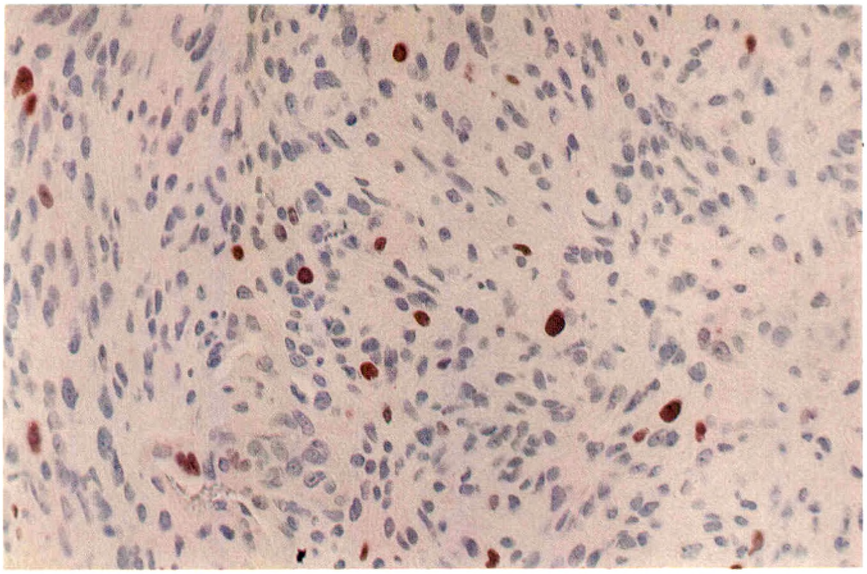


Fig 1. Acoustic neuroma stained for Ki-67, showing high proliferation with many positive nuclei (ABC method and hematoxylin, original x400).

strating antigens involved in cell proliferation have been introduced to determine TPF.[8-11] The nuclear antigen Ki-67 is expressed on all human proliferating cells throughout the cell cycle. Expression of this antigen occurs preferentially during the late G1, S1, G2, and M phases of the cell cycle, while the G0 (noncycling cells) phase consistently lacks the Ki-67 antigen.[12] Lesser et al[13] studied Ki-67 in 13 skull base tumors, 8 of which were small acoustic tumors. Two different growth rates were identified, the higher being fivefold the lower rate.

The aim of the present study was to examine the TPF in a series of acoustic neuromas expressed by Ki-67 in correlation to duration of symptoms.

MATERIALS AND METHODS

Twenty-eight tumors were randomly sampled from a series of 504 operated tumors. Half of the tumors occurred in patients having a short history and a symptom duration of less than 1 year, while the other half had a long history and a symptom duration of more than 5 years. Large tumors, cystic tumors, and neurofibromatosis-1 or neurofibromatosis-2 tumors were not included. Age at operation varied from 36 years to 71 years, with a mean age of 58.6 years.

The histopathologic diagnosis was reconfirmed, and a tumor block from each tumor was selected for immunohistochemical investigation. Seven tumors were excluded because the amount of tissue was considered too small. Age, symptom duration, and tumor size are depicted in Table 1.

TABLE 2. SYMPTOM DURATION VERSUS PROLIFERATION EXPRESSED BY KI-67 COUNTS IN PATIENTS WITH ACOUSTIC NEUROMAS

	No. of Patients		
Symptom Duration	*High Proliferation*	*Moderate Proliferation*	*Low Proliferation*
<1 year (n = 11)	6	4	1
>5 years (n = 10)	1	4	5

$p < .05$; χ^2 test.

IMMUNOHISTOCHEMISTRY

Formalin-fixed and paraffin-embedded tissue was used. Sections were cut at 3 to 5 μm, floated onto glass slides (Super Frost Plus, Menzel), and dried at 60°C for 20 minutes. After dewaxing, the slides were placed in 10 nmol/L citrate buffer (10 nmol/L citric acid monohydrate, pH 6.0, adjusted with 2N sodium hydroxide) and processed in a microwave oven 2 times for 5 minutes at 670 W. After cooling down at room temperature for 20 minutes and washing in tris(hydroxymethyl)-aminomethane–buffered saline (pH 7.6), the sections were stained according to the avidin-biotin-peroxidase complex (ABC) method, using the monoclonal antibody MIB-1 paraffin Ki-67 (Immunotech, Dianova) at a 1:50 dilution. The ABC was obtained from Dako, Copenhagen. The color reaction was developed with 3-amino-9-ethylcarbazole, and Mayer's hematoxylin was used for very slight counterstaining. Evaluation of the staining reaction was performed by 2 pathologists (P.E. and G.K.J.) independently, without knowledge of the clinical data. The number of positively stained nuclei was counted in the 10 high-power fields in which the number of stained nuclei appeared to be the highest, and the result was given as the average number. On the basis of the results of the counting, the tumors were divided into 3 groups of high, moderate, and low grades of proliferation, respectively. Staining and counting were performed twice with only minor differences.

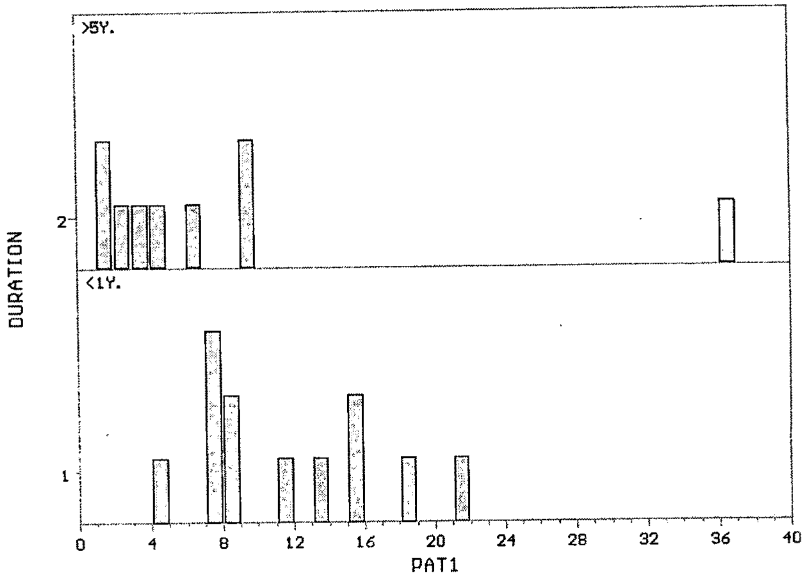


Fig 2. Histogram for proliferative counts of pathologist 1 (PAT1) by symptom duration.

RESULTS

All of the 21 acoustic neuromas studied were positively stained for Ki-67. The staining reaction appeared as a red staining of the nuclei with only a slight variation in color intensity. The results of the counting are shown in Table 1. Seven tumors were found to exhibit a high proliferation rate (Fig 1), 8 tumors a moderate rate, and 6 tumors a low rate.

Correlation Between KI-67 Staining and Symptom Duration. Fifteen tumors were evaluated as highly or moderately proliferative. A significant relation between short symptom duration (<1 year) and a high or moderate proliferative status was found in 11 tumors. Four tumors with a long symptom duration (>5 years) were found to be highly or moderately proliferative (high or moderate TPF). In 6 tumors classified as having a low proliferative rate, a significant relation between long symptom duration and low TPF was found in 5 tumors. One tumor with a short symptom duration was evaluated as poorly proliferative (Table 2).

Statistics. A statistical analysis of the results was performed in order to confirm or reject the hypothesis that a high proliferative cellular count occurs in tumors with a short symptom duration and that a low proliferative cellular count occurs in tumors with a long symptom duration.

Applying Wilcoxon's 1-sample rank sum test, we found a significant relation between the proliferative count and the symptom duration ($p = .02$; Fig 2).

To investigate the interobserver variation between the 2 pathologists' counting results, a *t* test was performed; LOGPROP = Log (PAT1/PAT2) as centered at 0 gave rejection with a $p = .004$ (Figs 3 and 4). However, the 2 pathologists' scoring was identi-

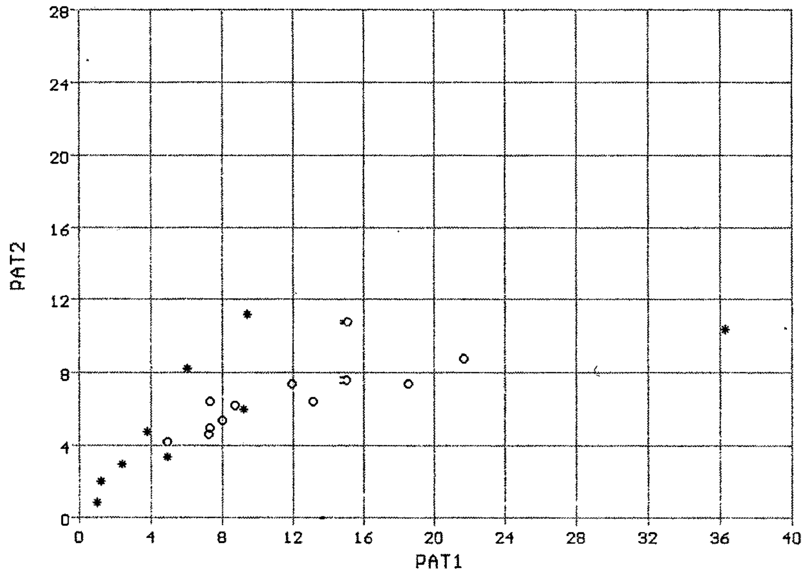
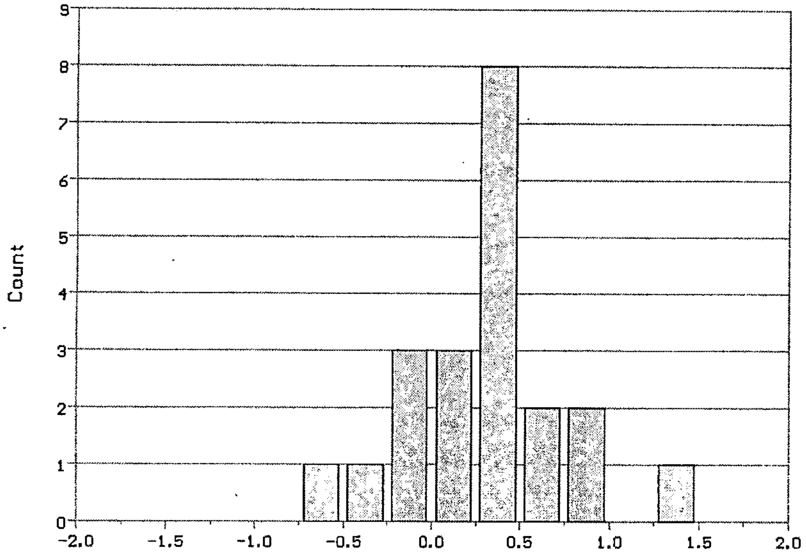


Fig 3. Pairs of scores by 2 pathologists.



cal in the group of tumors with a low rate of proliferation.

DISCUSSION

The Ki-67 nuclear antigen occurs in cells in the late G1, S1, G2, and M phases.[12] However, cells in constant proliferation or recycling are Ki-67–positive in the G1, S1, G2, and M phases. The main advantage of immunohistochemical staining compared to the previously applied labeling methods (eg, tritiated thymidine and bromodeoxyuridine) is that all of the proliferating cells, and not only those in the S phase, are markedly labeled. With the monoclonal antibody for use on routinely fixed and paraffin-embedded tissue, archival material for retrospective studies can be used. In addition, the preoperative injection procedure of thymidine labeling is avoided.

Although Ki-67 immunoreactivity may overestimate the TPF, several studies with astrocytic tumors indicate that it is a valuable tool for estimation of growth potential. There appears to be a good correlation between labeling indices and the histopathologic grade of astrocytic tumors.[14]

Previously, Ki-67 was studied in a group of 8 acoustic neuromas by Lesser et al.[13] Groups of high and low growth rates were identified, the high rate being fivefold the low rate. Previous clinical studies were of no value in estimating growth rates. The vast variation in the length of symptom duration did not correlate with the size of the tumor.[15]

In our study a significant relation between the duration of symptoms and TPF as represented by Ki-67 expression was observed. As in other studies,[7,15] we found no correlation between tumor size and symptom duration, emphasizing the fact that the growth rate of the tumor varies with time. This is in accordance with the statement of Olivecrona,[16] who claimed that the nature of the tumor left behind after incomplete surgery, rather than the amount of tumor left, dictated the subsequent fate of the patient.

Immunohistochemical investigations, including demonstration of Ki-67, can provide us with information concerning the TPF of an acoustic neuroma or a residual tumor. If the results obtained in our study are reproducible, it is possible that a better correlation between TPF and symptom duration can be achieved, and contribute to the decision of the surgeon who has to decide how radical the acoustic neuroma removal should be. One option will be that young patients with a short history and a high TPF could have radical operations, while tumors in older patients with a long history and a low TPF could be partially operated on, particularly if radical removal of the tumor would imply a high risk of a facial nerve lesion or other vital complications.

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CURRENT TRENDS, CONTROVERSIES, AND PERSPECTIVES IN RHINOLOGY AND SINUS SURGERY

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RECURRENT LARYNGEAL NERVE PARALYSIS DURING TRANSVENOUS INSERTION OF A PERMANENT ENDOCARDIAL PACEMAKER

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We present 2 patients with sudden onset of dysphonia due to acute unilateral vocal cord paralysis that occurred during transvenous insertion of a permanent endocardial pacemaker. Acute paralysis of the vocal cord due to this kind of medical intervention is a very unusual complication that has been rarely reported. We believe that traumatic insertion of a pacemaker through the subclavian vein triggered a dynamic process that led to vocal cord paralysis. Three hypothetic explanations are presented: 1) a direct vagus nerve lesion, 2) a direct inferior laryngeal nerve lesion, and 3) a central nervous system lesion caused by a cerebral microembolus. Physicians should be aware of the possibility that associated acute paralysis of the vocal cord may occur after transvenous insertion of an endocardial pacemaker.

KEY WORDS — endocardial pacemaker, nerve lesion, vocal cord paralysis.

INTRODUCTION

The most common form of direct cardiac pacing is endocardial; an electrode catheter is placed, usually in the right ventricle through the venous route. It is generally recognized that transvenous insertion of a permanent endocardial pacemaker entails minimal postoperative mortality of 1% to 3%.[1] The following complications after endocardial implants have been currently reported: thrombosis with embolization, bacterial endocarditis, perforation of the heart with tamponade, puncture of the subclavian artery, pneumothorax, tearing of the subclavian vein, and air embolism.[2] Neural lesions due to transvenous pacemaker implantation are uncommonly reported.

The development of vocal cord paralysis during the procedure of transvenous insertion of a permanent endocardial pacemaker is a very unusual complication, scarcely mentioned in the literature. Dedo and Dedo[3] mention that "transient and permanent vocal cord paralysis may occur following cardiac pacemaker implantation" without providing further information. Dieter et al[4] in 1981 and Copperman et al[5] in 1982 described recurrent laryngeal nerve paralysis following pacemaker introduction in 3 patients (total). The pacemaker was introduced in these cases through the cubital vein, through the internal jugular vein, and via subclavian vein puncture, respectively. The vocal cord paralysis was always ipsilateral to the venous insertion. No causative factor was found in these nerve injuries, and Copperman at al concluded that the recurrent nerve involvement remains an enigma.

Neural complications of transvenous cardiac pacing are scarcely reported. Isolated cases of phrenic nerve injury due to subclavian catheterization were described in the literature from 1970 to 1981.[4,6,7] We could find no report in the English-language, French, or German medical literature from 1983 to 1991 with regard to recurrent laryngeal nerve palsy occurring during transvenous insertion of a permanent endocardial pacemaker.

A discussion on neurovascular anatomy and neurologic pathology is essential to understand vocal cord paralysis.

Laryngeal motor paralysis of neural origin may be classified on the basis of site of lesion as central or peripheral. Peripheral paralyses involving the fibers of the laryngeal nerves from the surface of the medulla to the larynx are the most common type of laryngeal paralysis. They can be inflammatory, neuropathic, neoplastic, traumatic, or idiopathic.

The following cardiovascular lesions may involve the left inferior laryngeal nerve (ILN) by pressure or stretching exerted on the nerve by an aortic aneurysm, left auricular hypertrophy and dilatation from mitral stenosis, patent ductus arteriosus, or enlargement of the left pulmonary artery.

The disorders, on the basis of their relationship to the nucleus ambiguus, in which the upper and lower motor neurones synapse, are further classified as supranuclear (cortical and corticobulbar), nuclear (bulbar), or infranuclear (peripheral).[8,9] There is bilateral innervation from the motor cortex, and it is

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unusual for a central lesion to cause vocal cord paralysis. In this situation lesions must be diffuse and bilateral to produce a complete laryngeal motor paralysis. Cerebral concussion, congenital cerebral palsy, encephalitis, kernicterus, and diffuse cerebral arteriosclerosis are among those most often encountered.

Corticobulbar Paralysis. A lesion has to be in the area of decussation of the corticobulbar tract to produce a supranuclear laryngeal paralysis. This area is near the cranial end of the medulla. Basilar artery insufficiency and occlusion are the most common causes of a lesion at this point.

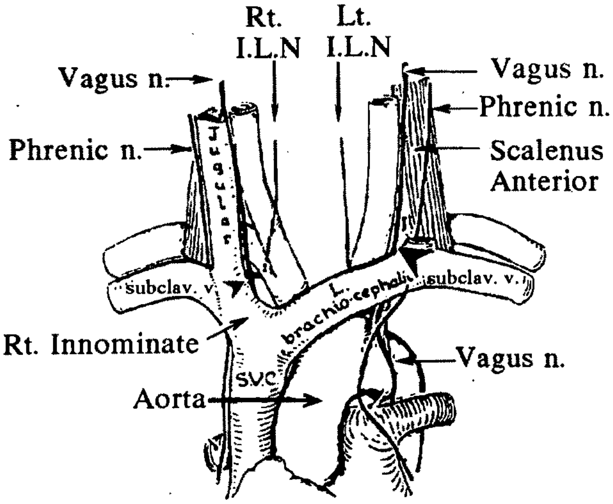
The nucleus ambiguus is the somatic motor nucleus of the 9th, 10th, and 11th cranial nerves. Cranially, the nucleus ambiguus is continuous with the motor nuclei of the 7th and 5th nerves. Caudally, each nucleus is continuous with the dorsolateral nucleus of the anterior horn of the spinal cord. The nucleus is approximately 2 cm long and begins at the upper border of the medulla. Because of the length of the nucleus it is possible that a localized lesion of the cranial or caudal portion could result in an isolated paralysis of the laryngeal muscles.[8]

Bulbar paralysis is due to the destruction of all or part of the nucleus ambiguus in the medulla. Insult to the area around the nucleus ambiguus results in a combined superior and recurrent laryngeal nerve paralysis of the flaccid type.[9]

The most common cause is vascular insufficiency due to occlusion of 1 of the following arteries: vertebral, posterior inferior cerebellar, anterior inferior cerebellar, and superior, middle, and inferior lateral medullary branches. Other causes of bulbar paralysis are progressive bulbar paralysis, multiple sclerosis, syringobulbia, syphilis, rabies, encephalitis, poliomyelitis, and intramedullary tumors.

Vagus Nerve. Most fibers of the ILN travel with the main trunk of the vagus. The vagus leaves the nodose ganglion to pass inferiorly down the neck, lateral to the internal and common carotid arteries lying between the internal jugular vein and the internal carotid artery, and then between the same vein and the common carotid artery until it reaches the root of the neck.

On the right side the vagus nerve continues downward behind the internal jugular vein and crosses the first part of the subclavian artery, enters the thorax, and descends through the superior mediastinum (see Figure). On the left side, the vagus enters the thorax between the left common carotid and left subclavian arteries, and behind the left brachiocephalic vein. It descends through the superior mediastinum, crosses the left side of the aorta, and passes behind the root of the lung.



Hypothetic points of lesion of inferior laryngeal nerve (ILN) and vagus nerve by subclavian introduction of pacemaker. Small arrowhead shows point at which right ILN is vulnerable as it courses around subclavian artery on right. Minor venous trauma can lead to bleeding and secondary pressure, lead to stretching on nerve that loops around subclavian artery, or induce disturbance of vascular supply of nerve. In this area, injury of vagus nerve is possible, too, through microperforation of subclavian vein or brachiocephalic vein. Large arrowhead shows area in which injury of vagus nerve through microperforation of subclavian vein or brachiocephalic vein is possible. SVC — superior vena cava.

The right ILN recurs around the right subclavian artery. The left ILN travels a similar course, except that it is carried further into the thorax. The nerve arises on the anterior surface of the arch of the aorta, just inferior to the interspace between the origins of the left common carotid and subclavian arteries. As the nerve loops under the arch of the aorta, it is distal to the attachment of the ligamentum arteriosum to the concavity of the arch, and then it ascends to the side of the trachea (see Figure).

Vascular Supply and Anatomy Related to Vagus Nerve. The first part of the left subclavian artery arises from the arch of the aorta, behind the left common carotid artery.[10] On the left side of the neck the 4 branches of the artery — vertebral, internal thoracic (mammary), thyrocervical trunk, and costocervical trunk — arise from the first part of the subclavian artery.

The vertebral artery arises from the upper and posterior part of the first part of the subclavian artery. The vertebral artery runs upward, pierces the dura and the arachnoid mater, ascends in front of the roots of the hypoglossal nerve, and inclines medially to the front of the medulla oblongata, where, at the lower border of the pons, it unites with the vessel of the opposite side to form the basilar artery.

The branches of the vertebral artery within the cranium are the meningeal branches, the posterior spinal artery, the anterior spinal artery, the posterior inferior cerebellar artery (PICA), and the medullary arteries. It is to be noted that the PICA supplies the lateral part of the medulla. Thrombosis of this artery will therefore cause the "lateral medullary syndrome," with loss of function of the nucleus ambiguus, nucleus solitarius, vestibular and cochlear nuclei, spinocerebellar tracts, lateral spinothalamic tract, spinal nucleus, and tract of the trigeminal nerve.

The vascular area involved during pacemaker insertion and its vulnerable relationship with the vagus nerve is as follows.

The brachiocephalic veins (innominate veins) are each formed by the union of the internal jugular and subclavian veins of the corresponding side (see Figure). The right brachiocephalic vein is about 2.5 cm long, begins behind the sternal end of the right clavicle, passes almost vertically downward, and joins the left brachiocephalic vein to form the superior vena cava, close to the right border of the sternum. The right brachiocephalic vein lies in front of the brachiocephalic artery and the right vagus nerve. The left brachiocephalic vein is longer that the right one (about 6 cm long), begins behind the sternal end of the left clavicle, runs obliquely to the right and downward behind the upper half of the manubrium sterni, and unites with the right brachiocephalic vein to form the superior vena cava (see Figure). It lies in front of the subclavian and common carotid arteries and superficially crosses the left phrenic nerve, vagus nerve, and brachiocephalic artery. The arch of the aorta lies below the vessel (see Figure).

Two cases of acute-onset dysphonia, which appeared synchronously with the transvenous insertion of a pacemaker, are the subject of our presentation.

CASE REPORTS

Case 1. In 1988, a 76-year-old man underwent transvenous insertion of a permanent endocardial pacemaker through the left cephalic vein. The procedure was performed under local anesthesia. The patient was speaking with his physician during the insertion of the catheter. Concomitantly with the insertion he felt a sudden change in the sound of his voice. An instantaneous dysphonia was noted by himself and by the cardiologist. The procedure was accomplished as planned without any other problems. Indirect laryngoscopy revealed abduction paresis of the left vocal cord. The cord was bowed laterally, and a glottic chink of 2 mm persisted during phonation. The patient experienced saliva aspiration. Clinical examination of the neck did not reveal any disorder of the thyroid gland or other unusual findings.

Results of an iodine 131 scan of the thyroid and blood laboratory values were normal. There were no other neurologic disturbances. A computed tomographic examination did not reveal a mediastinal mass or lymph node hyperplasia. On further examinations 6, 12, and 24 months later, the vocal cord was found to lie in a paramedian position with no compensation.

Case 2. In 1989, a 72-year-old man underwent transvenous insertion of a permanent endocardial pacemaker through the right cephalic vein. The procedure was performed under local anesthesia. The patient was talking with his physician during the introduction of the pacemaker. He suddenly felt a change in the sound of his voice, and a sudden dysphonia was noted by himself and by the cardiologist. The procedure was accomplished as planned without any other problems.

Indirect laryngoscopy revealed abduction paresis of the right vocal cord. The cord was bowed laterally and flaccid, and a glottic chink of 2 to 3 mm persisted during phonation. The patient experienced saliva aspiration. Anterior prolapse of the arytenoid was not observed. The voice was weak, breathy, and hoarse, and air escaped between the cords during phonation.

On further examinations 6 and 14 months later, there was no compensation found. Clinical inspection of the neck did not reveal any disorder of the thyroid gland or other unusual findings. An iodine 131 scan of the thyroid and blood laboratory tests showed normal results. There were no other neurologic disturbances. Computed tomographic examination did not reveal a mediastinal mass or lymph node hyperplasia.

DISCUSSION

In the 2 cases described, dysphonia appeared in the midst of the transvenous insertion of a permanent endocardial pacemaker. The patients heard and were aware of the sudden dysphonia, being able to pinpoint the exact time when it appeared. On laryngoscopy a paramedian vocal cord position with flaccid cord paralysis was diagnosed in both patients.

Viral neuritis, peripheral neuropathy associated with diabetes mellitus, collagen disease, metastatic mediastinal carcinoma, and laryngeal carcinoma were excluded. Because of the sudden onset of the paralysis, which appeared concomitantly and during the same operative procedure, we think that the transvenous insertion was the direct causative agent. In neither of these 2 cases could we find another clear and obvious explanation for the sudden vocal cord paralysis. We suggest the following hypothetic explanations.

Injury of Vagus Nerve. On the left side the vagus nerve enters the thorax between the left common carotid and left subclavian arteries, and behind the left brachiocephalic vein (see Figure, large arrowhead). An injury of the nerve through a microperforation of the subclavian vein or brachiocephalic vein could occur in this area. This trauma leads to bleeding, hematoma, and secondary pressure on the nerve, or to a lesion of the vascular supply of the vagus nerve. On the right side, the vagus nerve enters the thorax between the subclavian artery posteriorly and the right brachiocephalic vein, which is situated anteriorly (the subclavian jugular vein angle). A microperforation of the subclavian or brachiocephalic vein could be produced in this area (see Figure, small arrowhead).

Injury of Inferior Laryngeal Nerve. The anatomy of the right ILN makes it vulnerable to injury as it courses around the subclavian artery on the right. Paralysis of the right ILN may ensue from traumatic catheterization in the subclavian jugular vein angle (see Figure, small arrowhead). This minor venous trauma can lead to bleeding.

Microembolism. Microembolism (air embolism, thrombus) may reach the brain through an undiagnosed patent foramen ovale to the region of the PICA blood supply during the pacemaker introduction. Central nervous system lesions account for approximately 10% of all laryngeal motor paralysis lesions.[4] It is known that not the whole nucleus ambiguus is necessarily destroyed by microembolism. Because of the segmental localization of the cell groups in the nucleus ambiguus,[8,11] it is possible to have an isolated paralysis of the sensor, abductor, or adductor muscle groups.

CONCLUSIONS

Most of the motor fibers ending in the larynx travel with the main trunk of the vagus. In their course from the brain stem to the larynx they follow a path that brings them in proximity to numerous anatomic structures. Pressure on or disruption of these structures may cause a disorder of the vagus and of the recurrent laryngeal nerve. We consider that in our cases a traumatic insertion of the pacemaker through the subclavian vein triggered a dynamic process that led to vocal cord paralysis. Considering the proximity of the vagus nerve and the ILN to the sites of pacemaker insertion, it is surprising that vocal cord paralysis has not been reported more often. Three hypothetic explanations for this unusual neural complication are suggested above.

Although acute paralysis of a vocal cord during transvenous insertion of permanent endocardial pacemaker is a very rare complication that has not been often reported, laryngologists and cardiologists should be aware of and alerted to the possibility of this phenomenon.

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DEXAMETHASONE INHIBITION OF THE DEVELOPMENT OF DYSPLASTIC BONY LESIONS IN LP/J MICE

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Inbred LP/J mice have been observed to spontaneously develop abnormal bony lesions of the ossicles and otic capsule that progress throughout the life of the animals. This genetically inherited murine disorder produces bony lesions that share some gross and histologic features with bony lesions seen in human tympanosclerosis. Previous studies on LP/J mice have demonstrated evidence of immunologically mediated injury in the progression of the newly forming bony lesions. This study was designed to examine the effects of dexamethasone on the development of the bony lesions in LP/J mice. The purpose was to attempt to elucidate the relationship of the immunologic injury observed in earlier studies and the progression of the dysplastic bony lesions. The results show that LP/J mice treated with dexamethasone developed significantly fewer dysplastic bony lesions compared to the age-matched, saline-treated controls. There was also a statistically significant difference in the quantity and cellularity of the middle ear effusions between the experimental and control animals.

KEY WORDS — dexamethasone, ear disease, inbred strain mice, temporal bone, tympanosclerosis.

INTRODUCTION

Histologic examination of the bony skeleton of LP/J mice has demonstrated the presence of abnormal bony lesions, limited to the temporal bones, in almost all of the animals by 90 weeks of age.[1] The bony lesions tend to begin at 2 months of age and progress in size and prevalence throughout the life of the animals. The progressive nature of the disease is supported by audiometric data,[2] histologic sampling at multiple ages,[1,3] and sequential fluorochrome marker studies.[4]

The following sequence of events is suggested by examination of over 200 temporal bones ranging in age from 4 to 72 weeks, using light microscopy, electron microscopy,[5] and immunohistology.[6] The lesions appear to begin in the submucosa and areas of ossicular bone resorption as a relatively acellular disarray of collagenous matrix. The lesions then increase in cellularity and take on a poorly organized osteoid appearance, staining eosinophilic with hematoxylin and eosin. Calcospherites are demonstrated with transmission electron microscopy at the interface of calcified and uncalcified bone matrix. Finally, the mature lesions calcify completely and appear to be mature sclerotic bone.

Immunologically mediated injury is believed to play a significant role in the pathogenesis of these dysplastic bony lesions. This hypothesis is supported by the observation of an immunoglobulin-containing fluid layer in the middle ear coating the middle ear mucosa and ossicles preceding the development of the bony lesions.[6] This is followed by increasing cellular infiltrates of monocytes, macrophages, and lymphocytes, which would be predicted with antigen-antibody complex formation and activation of the complement cascade. In addition, prominent staining for IgG and IgM was observed in the early osteoid lesions, and subperiosteal immunoglobulin deposition was seen in areas of maturing lesions.[6] Immunohistologic techniques have also documented the presence of C3 in the middle ear effusions (Brodie, unpublished results). Acute otitis media with polymorphonuclear infiltrates is no more common in LP/J mice than in other strains of mice.

This study was designed to examine the effects of dexamethasone on the development and progression of the bony lesions in LP/J mice. It was initiated in an attempt to elucidate the relationship of the immunologically mediated events reported in earlier studies to the dysplastic bony lesions. Does inhibition of the early immunologic events, preceding the bony lesion formation, diminish dysplastic bone formation?

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Presented at a poster session of the meeting of the Association for Research in Otolaryngology, Clearwater Beach, Florida, January 31–February 4, 1988.

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METHODS

Fifteen LP/J mice and 4 CBA/J mice (a control strain without middle ear bony changes) were included in the study. The LP/J mice were first-generation offspring from the parental stock obtained from Jackson Laboratory, Bar Harbor, Me. The first group, consisting of 7 LP/J mice and 4 CBA/J mice, was treated weekly, from the time of weaning, with 1.5–mg/kg body weight intramuscular injections of suspension dexamethasone acetate (Decadron LA). The second group, consisting of 4 LP/J mice, received biweekly intramuscular injections of suspension dexamethasone acetate, also 1.5 mg/kg body weight. The third group, consisting of 4 LP/J mice, received weekly intramuscular injections of sterile normal saline. The animals were sacrificed at 6 months of age by intraperitoneal injection of a lethal dose of sodium pentobarbital. The temporal bones were harvested and an opening was made into the ventral bullae. The bullae were filled with B5 fixative (6% mercuric chloride with 1.25% sodium acetate in distilled water mixed 9:1 with 37% formalin) and immersed in the fixative for 2 to 4 hours, rinsed in phosphate-buffered saline, and decalcified overnight in 1.35N hydrochloric acid plus 0.003 mol/L chelating agent (Cal X; Fisher Scientific Products). The specimens were processed and embedded in paraffin by means of an Ames VIP tissue processor. The tissue was serially sectioned at 4 μm on a rotary microtome, and every fifth section was mounted on a slide coated with 0.5% white glue (Elmer's). Every fifth slide was then stained with hematoxylin and eosin, coverslipped, and examined under an Olympus BH microscope. A Vias image analysis system was used to quantify the cross-sectional area of the lesions.

The murine temporal bones were rated on a scale of 0 to 4 based on the number of small ($<200\ \mu m^2$), intermediate (200 to 500 μm^2), and large ($>500\ \mu m^2$) dysplastic bony lesions in the otic capsule and ossicles: 0 for no lesions; 1 for 1 small lesion; 2 for 2 small lesions or 1 intermediate lesion; 3 for 1 large lesion, or 1 intermediate and 1 small lesion, or 3 small lesions; and 4 for anything more. The experimenter evaluating the bony lesions was blinded to the treatment group and mouse strain. The middle ear effusions were also rated on a scale of 0 to 4 based on the quantity of effusion and degree of cellularity.

RESULTS

There were 8 temporal bones examined from LP/J mice treated with normal saline, 14 LP/J temporal bones from animals treated with a low dose of dexamethasone, and 8 LP/J temporal bones from mice treated with a high dose of dexamethasone. Eight temporal bones from CBA/J mice treated with a low dose of dexamethasone were also examined. Histologically, the lesions were exophytic dysplastic bony tissue, most commonly adjacent to the incudostapedial joint and associated with middle ear effusions (Fig 1). The effusions contained monocytes, multinucleated giant cells, occasional polymorphonuclear cells, and frequent calcium concretions. The dysplastic bony lesions ranged from poorly organized eosinophilic hypocellular matrix to a basophilic, more cellular remodeling bone. There were no qualitative differences in the histologic appearance of the bony lesions among the 3 treatment groups.

In the normal saline–treated group, 7 of 8 temporal bones (87.5%) contained bony lesions, and all of the middle ears contained effusions. The mean rating score of the lesions was 2.6, and the mean score for the effusions was 2.9. Eight of 14 temporal bones (57.1%) from LP/J mice treated with low-dose dexamethasone contained lesions, with a mean rating score of 1.3. Seventy-one percent of the middle ears contained effusions, with a mean score of 1.2. In the high-dose dexamethasone group, only 3 of 8 temporal bones (37.5%) contained lesions, with a mean score of 0.9. Sixty-three percent of the middle ears contained effusions, with a mean score of 1.4. These results are graphically represented in Fig 2. The CBA/J mice developed no bony lesions. Two of the middle ears contained mild effusions, and 1 contained a purulent exudate. An analysis of variance was performed on the 3 groups of LP/J mice, demonstrating a significant overall effect of the steroid treatment on the development of bony lesions ($F_{2,27} = 3.25$, $p = .05$) and on the degree and characteristics of the effusions ($F_{2,27} = 4.99$, $p = .01$).

DISCUSSION

The LP/J mouse has a genetically inherited disorder that results in the progressive development of dysplastic bony lesions limited to the ossicles and otic capsule.[1,3] Earlier work has demonstrated a gradually developing middle ear effusion that coats the ossicles and contains progressive cellular infiltrates of macrophages and monocytes, but with minimal polymorphonuclear cells. The effusions have been demonstrated to contain both immunoglobulins and complement. In addition, in the earliest phase the bony lesions stain quite intensely for the presence of IgG and IgM.[6] These studies have strongly suggested that immunologic injury plays a central role in the development of these bony lesions.

The present study was designed to examine the effect of steroid immunosuppression on the sequen-

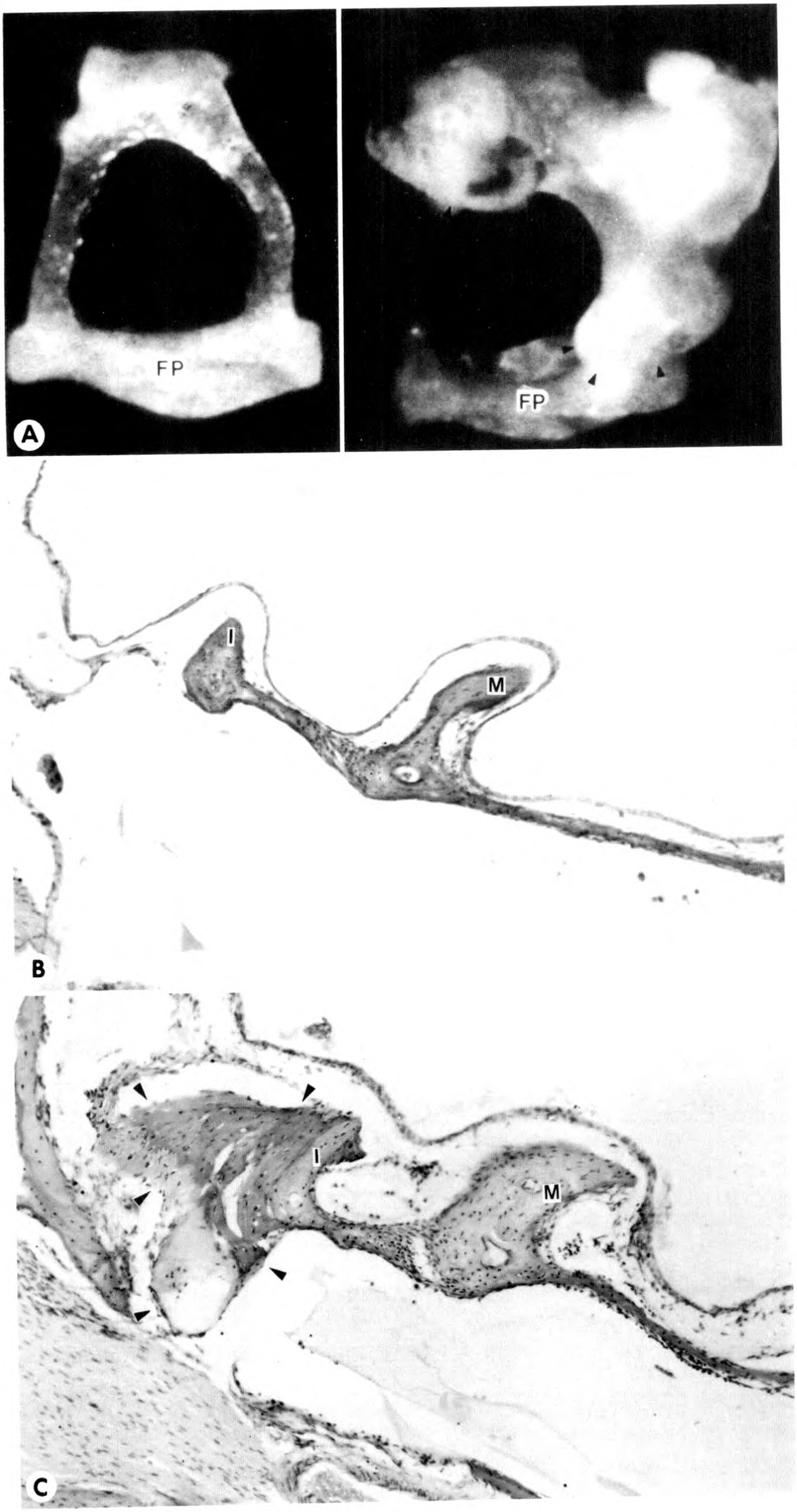

Fig 1. A) Gross photograph of dysplastic bony lesions (arrowheads) involving ossicles of LP/J mouse. FP — footplate. B) Histologic section containing normal LP/J incus (I; paraffin, H & E). M — malleus. C) Histologic section containing LP/J incus (I) manifesting gross dysplastic bony lesions (arrowheads; paraffin, H & E). M — malleus.

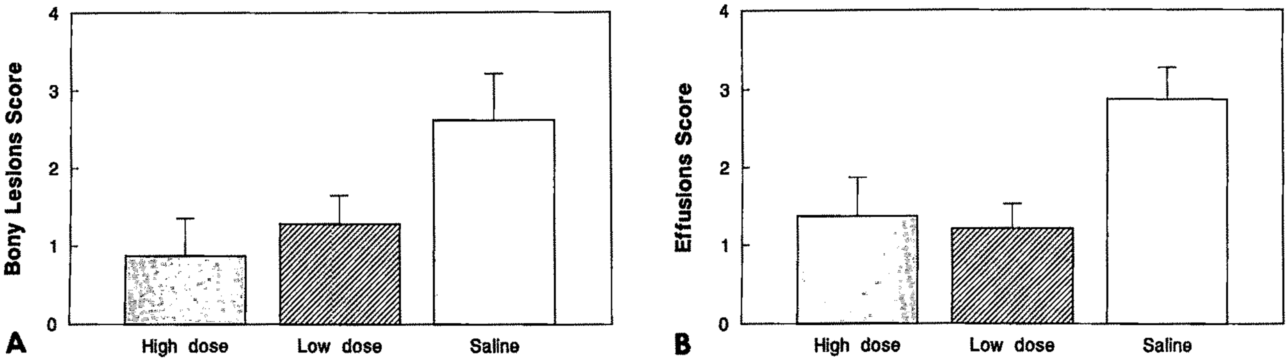

Fig 2. Mean A) bony lesion rating scores and B) effusion rating scores are plotted for normal saline control group, low-dose dexamethasone treatment group, and high-dose dexamethasone treatment group.

tial development of middle ear effusions, cellular infiltrates, and bony lesions in LP/J mice. The study demonstrated a decrease in the incidence and size of the dysplastic bony lesions, as well as decreased cellular infiltration in the effusions of mice treated with dexamethasone. These results further support the hypothesis that the dysplastic bony lesions in LP/J mice result from immunologically mediated injury, suppression of which decreases the manifestations of the disease.

A second potential effect of the dexamethasone on the development and progression of the bony lesions arises from its property of inhibition of collagen synthesis. As has been demonstrated in previous studies, one of the early histologic changes observed in the development of these bony lesions is submucosal and subperiosteal deposition of a disorganized array of collagen fibers.[5] Calcospherites are deposited in this hypocellular matrix and coalesce, and subsequent bone remodeling occurs. Interruption of the initial collagen deposition with dexamethasone may suppress further bony lesion development.

There are many human diseases that cause dysplastic bony lesions in the middle ear and otic capsule, two of which are tympanosclerosis and otosclerosis. The lesions in both of these disorders share many histologic similarities with the murine disease as examined under light and electron microscopy.[1,3,6] Although the earlier descriptions of the LP/J mouse compared it to otosclerosis, subsequent investigations revealed much greater similarity between this murine model and tympanosclerosis.[5,6] The relationship of tympanosclerosis to chronic inflammation has been long established, but recent evidence supports the possibility of immunologically mediated injury in the pathogenesis of the bony lesions and tympanic membrane plaques.[7,8] Less evidence exists linking otosclerosis to autoimmune injury. Some preliminary work has suggested the possibility of autoimmunity to type II collagen in otosclerosis.[9] However, subsequent studies have refuted these earlier findings.[10,11] If future research more clearly establishes immunologically mediated injury in the pathogenesis of these disorders, immunosuppression may play a role in inhibiting the development of the bony lesions, as was successfully accomplished in this murine model.

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IMAGING CASE STUDY OF THE MONTH

UNILATERAL ACOUSTIC NEUROMA ASSOCIATED WITH A TENTH CRANIAL NERVE SCHWANNOMA

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The concomitant occurrence of an acoustic neuroma and a schwannoma of the jugular foramen is an uncommon condition. According to the diagnostic criteria proposed by the National Institutes of Health Consensus Development Conference Statement,[1] this association can be observed in patients affected by neurofibromatosis types 1 (NF-1) and 2 (NF-2). However, no case in which the family history is negative for these genetic diseases has been previously reported in the literature, to the authors' knowledge. Thus, it has been considered worthwhile to present 1 case with this particular and unusual characteristic and to emphasize the ability of magnetic resonance imaging (MRI) in evaluating this condition.

CASE REPORT

A 52-year-old man presented with a 1-year history of episodic unsteadiness without vertigo or tinnitus in the left ear. Speech audiometry was normal. Pure tone audiometry showed a 30-dB, left-sided, high-

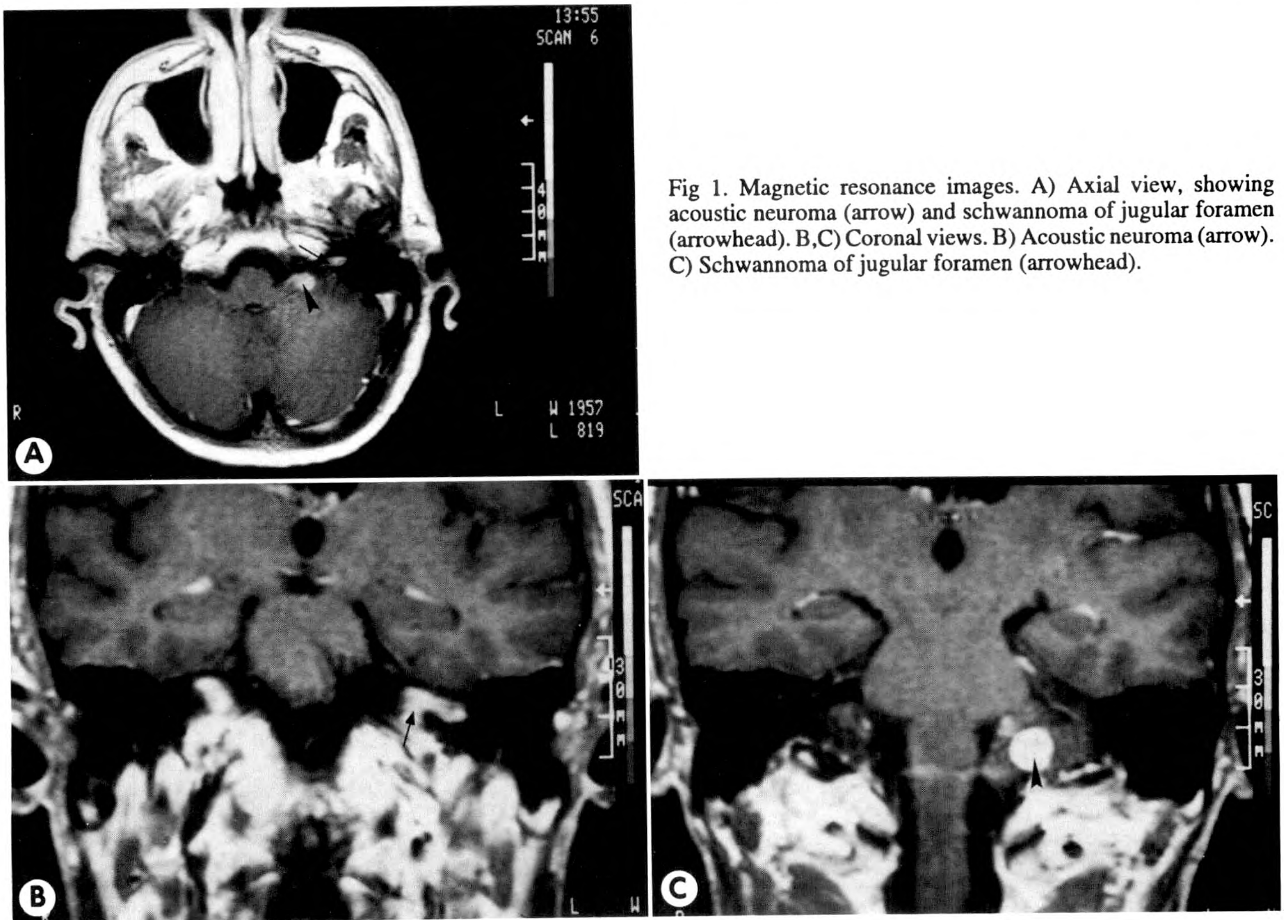

Fig 1. Magnetic resonance images. A) Axial view, showing acoustic neuroma (arrow) and schwannoma of jugular foramen (arrowhead). B,C) Coronal views. B) Acoustic neuroma (arrow). C) Schwannoma of jugular foramen (arrowhead).

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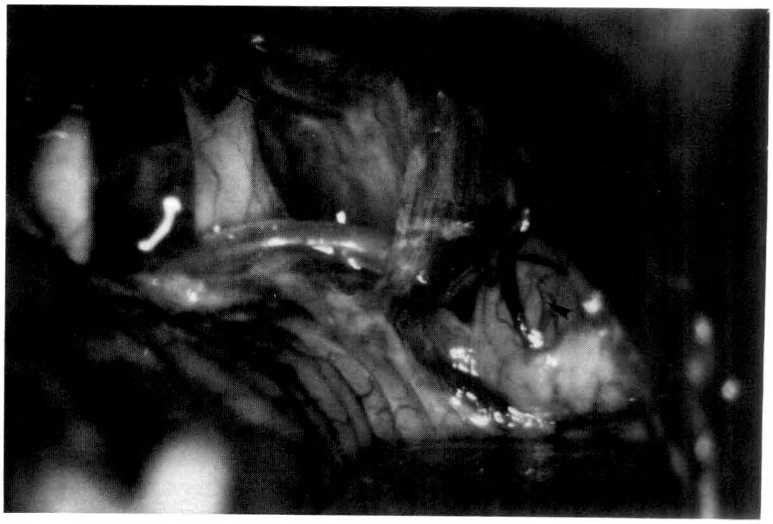

Fig 2. Intraoperative view of acoustic neuroma protruding toward cerebellopontine angle (arrow), and schwannoma of 10th nerve (arrowhead).

tone sensorineural hearing loss. The auditory brain stem response was abnormal, with poorly formed and delayed waves in the affected ear. Electronystagmography revealed a significantly reduced left caloric response and significant right-beating nystagmus.

Gadolinium-enhanced MRI of the posterior fossa was performed (Fig 1). The MRI coronal and axial scans revealed enlargement of the left intracanalicular nerve trunk, suggesting an acoustic neuroma. This tumor was associated with another 1-cm enhancing mass located on the left jugular foramen. Despite a negative family history for NF-2 and other associated neural lesions such as café au lait spots (indicative of von Recklinghausen's disease or NF-1), MRI of the entire neuraxis spinal cord as well as the brain was obtained. The MRI showed no other tumors within these structures.

Surgery by the retrosigmoid approach (Fig 2) accomplished total removal of both lesions. The facial and cochlear nerves, as well as cranial nerves IX, X, and XI, were preserved. The postoperative course was uncomplicated, with preservation of preoperative levels of hearing.

Histologic findings demonstrated that the intracanalicular tumor was an acoustic neuroma, while the jugular foramen mass was a schwannoma of the 10th nerve.

DISCUSSION

The emergence of gadolinium-enhanced MRI has significantly improved the early detection of intracanalicular tumors. It has become the imaging modality of choice for the evaluation of suspected cerebellopontine angle lesions.[2] It has proven to be valuable in diagnosing acoustic neuromas of less than 1 cm in size. In our case, the mode of clinical presentation was diagnostically helpful, with typical audiologic findings of eighth nerve involvement. The MRI confirmed our suspicion of acoustic neuroma, but it also allowed us to detect another tumoral mass, clinically asymptomatic, in the jugular foramen.

This tumor rose from the 10th cranial nerve in the pars nervosa of the jugular foramen and gave histologic evidence of being a schwannoma.[3] Reviewing the literature, we find that the association of an acoustic neuroma with a schwannoma is possible in NF-1 and NF-2[1] (genetic diseases linked to a defect of chromosomes 17 and 22, respectively).

Our patient had a negative family history and did not meet the diagnostic criteria for NF-1 or NF-2. He represents an illustrative case of the early diagnosis provided by MRI scanning. This ability has been generally recognized as the best chance of preserving cranial nerve function at surgery. The successful preservation of hearing and facial and vagal functions in our case substantiates the importance of this diagnostic tool in preventing and reducing postoperative complications.[4]

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IMAGING CASE STUDY OF THE MONTH

FIBROSARCOMA OF THE POSTERIOR NECK

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INTRODUCTION

Fibrosarcomas are malignant neoplasms characterized histologically by spindle cells, with a pattern of interlacing fascicles and categorized into low and high grades according to the degree of differentiation. Although fibrosarcomas may occur anywhere in the body that its progenitor cell, the fibroblast, exists, fewer than 5% of these tumors present in the head and neck.[1]

We present a case study of a fibrosarcoma of the posterior neck in order to define the value of magnetic resonance imaging (MRI), computed tomography (CT), and magnetic resonance angiography (MRA) in planning treatment for this neoplasm.

CASE REPORT

A 21-year-old man presented to our clinic with a 9-month history of a slowly enlarging 9 × 7-cm firm, immobile, and nontender mass of the left posterior neck. Three years previously he had suffered subluxation injury in a motor vehicle accident resulting in a Brown-Sequard and central cord syndrome. At that time he was surgically treated with posterior cervical fusion, with nearly complete return of function. The presence of an enlarging mass 5 cm lateral to the previous surgical site 3 years later prompted evaluation by CT, which visualized a left-sided neck mass posterolateral to the cervical spine without bone, carotid artery, or jugular vein involvement. Incisional biopsy demonstrated a nodular fasciitis versus a low-grade fibrosarcoma.

After referral to our institution, MRI with MRA confirmed a soft tissue mass with moderate vascularity (see Figure). Additionally, it noted close proximity to the left vertebral artery, but no intraspinal canal involvement.

At time of resection the tumor approximated but did not invade the vertebral column. The tumor was excised with grossly clear margins, sparing the spinal accessory nerve and spinal roots C-4, C-5, and C-6. The final pathologic evaluation determined a low-grade fibrosarcoma with positive microscopic margins. Consultation with the neurosurgery and radiation oncology departments and the family yielded the consensus that further surgery to obtain microscopic free margins would cause significant morbidity. The patient therefore received postoperative radiotherapy.

DISCUSSION

Fibrosarcoma is a primary malignant fibroblastic tumor with fibrous intercellular substance in which no osteoid or cartilage is formed. Traditionally, fibrosarcoma has been reported as the most common soft tissue sarcoma in the head and neck in adults,[1] and it ranks second only to rhabdomyosarcoma in the pediatric age groups.[2] However, recent improvements in immunohistochemical and electron microscopic techniques have allowed more precise histopathologic diagnoses, leaving a smaller percentage of head and neck neoplasms as true fibrosarcomas.[1-3] Many of these previously diagnosed fibrosarcomas were subsequently reclassified under stricter criteria.

Fibrosarcoma can occur at any age and at any site in the head or neck. Most patients present with painless masses, most commonly in the lateral neck or paranasal sinuses, in a relatively equal male to female distribution. Frankenthaler et al[3] and others[4] have suggested an apparent association with prior irradiation (10%), mechanical trauma (4%), and thermal trauma (0.8%) at the tumor site. Our patient's case was associated with mechanical trauma.

Pathologically, fibrosarcomas in most series are divided into either low-grade or high-grade lesions.[3,4] Low-grade fibrosarcoma is defined by sheets of uni-

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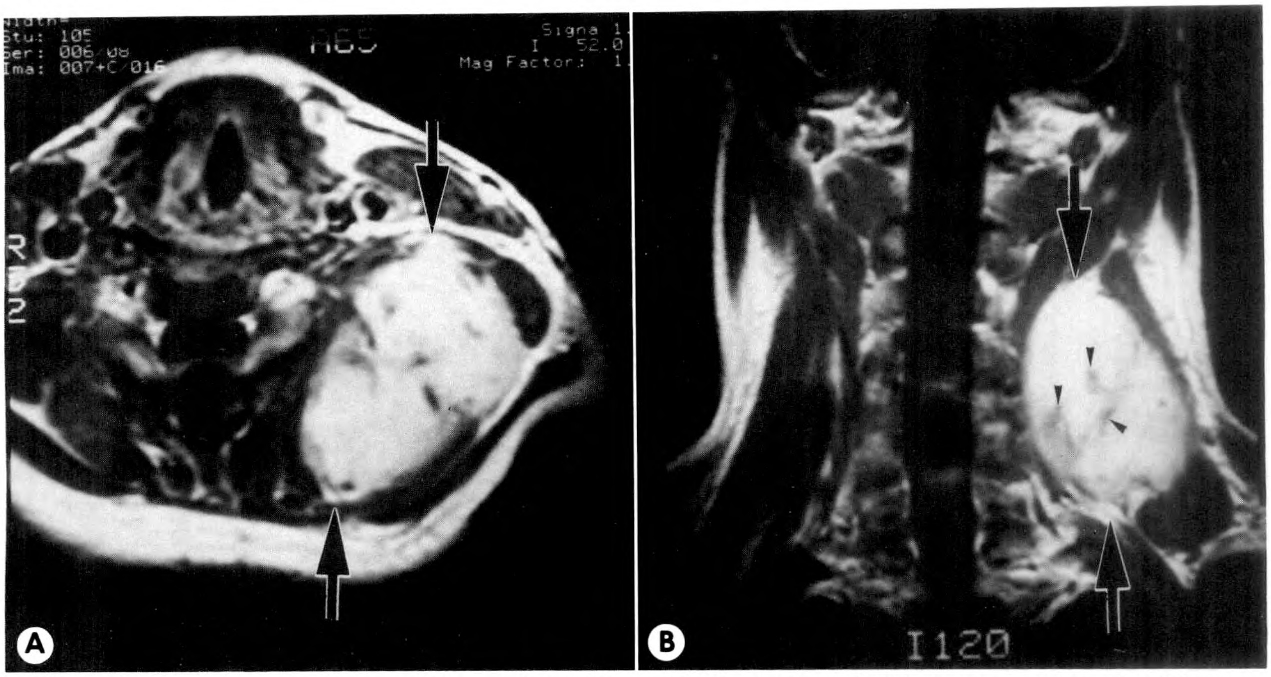

Enhanced magnetic resonance images of lower neck revealing large high-signal mass in left paravertebral area. A) Axial view shows large anteroposterior diameter (arrows). B) Coronal view shows vertical length (arrows). Scalene muscle separation is produced by mass. Flow voids in center of mass reflect vascularity of lesion (arrowheads).

form spindle cells with moderate cellularity arranged in a herringbone pattern, mild nuclear pleomorphism, and rare mitoses. A collagenous stroma is usually present. High-grade lesions show greater nuclear pleomorphism, abundant cellularity, frequent mitotic activity, and possibly tumor necrosis. The pathologic differential diagnosis of fibrous and spindle cell tumors in the head and neck includes neurofibrosarcoma, dermatofibrosarcoma protuberans, nodular fasciitis, monophasic synovial sarcomalike neoplasm, and malignant fibrous histiocytoma.[1-3]

The treatment of choice remains wide local excision. This complete surgical resection can be difficult, since many of these tumors appear to be enveloped by a pseudocapsular membrane with microscopic fingerlike extensions of tumor, which characterizes the infiltrative character of the lesion. As a result, simple excision of fibrosarcomas is often followed by local recurrence. Preoperative radiographic assessment is critical for planning treatment. The role of CT and MRI is largely to determine the anatomic borders so that the extent of surgical excision can be anticipated.

When a patient is found to have central necrosis or deeply invasive extension by either CT or MRI, a more radical surgical resection may be planned. This allows preoperative patient counseling as to the possible deficits that may result from the operation.

This case illustrated the clear advantage of MRI over CT. Magnetic resonance imaging demonstrated superior soft tissue discrimination, better definition of the extent of the lesion, multiplanar images, and the lack of irradiation artifact from the metallic implants from previous spinal surgery.

In this case MRI with MRA was able to delineate the extent of the tumor mass and define its relationship to the surrounding neurovascular structures, such as the vertebral artery and cervical nerve rootlets, without conventional angiography. These findings prompted a preoperative neurosurgical consultation to assist in planning the paraspinal dissection. Linear signal voids within the mass on MRI allowed a preoperative assessment of the vascularity of the tumor.

A consensus among most series shows that grade and tumor size are important prognostic factors, correlating with survival and recurrence rates.[1,3,4] However, the adequacy of surgical margins is probably the most critical prognostic factor. Conley et al[4] showed that the number of local recurrences was "astounding" and that they were related to inadequate surgery. These above factors underline the importance of preoperative radiographic imaging to effectively plan therapy.

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TWENTY-NINTH POSTGRADUATE COURSE IN EAR SURGERY

The 29th Postgraduate Course in Ear Surgery will be held April 10-15, 1994, in Nijmegen, the Netherlands. For more information, contact Prof dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax 80-540251.

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The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone (303) 788-4320 or (303) 850-9545; fax (303) 788-4234.

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PATHOLOGY CONSULTATION
SQUAMOUS ODONTOGENIC TUMOR

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The squamous odontogenic tumor is almost exclusively an intraosseous lesion of the jaw bones. Only 1 extraosseous variant has been reported. The tumor is histologically benign, with only occasional recurrences after surgical removal. Malignant alteration is unknown, but the lesion must be distinguished from intraosseous squamous cell carcinomas.

The squamous odontogenic tumor exists in 3 clinicopathologic forms. The most common arises within the gnathic bones and is considered to arise in the periodontium. Since the original description in 1975,[1] there have been 32 acceptable cases of this tumor reported in the English-language journals.[2] A so-called mural form (12 cases) develops in association with odontogenic cysts.[2,3] Baden et al[2] reported the

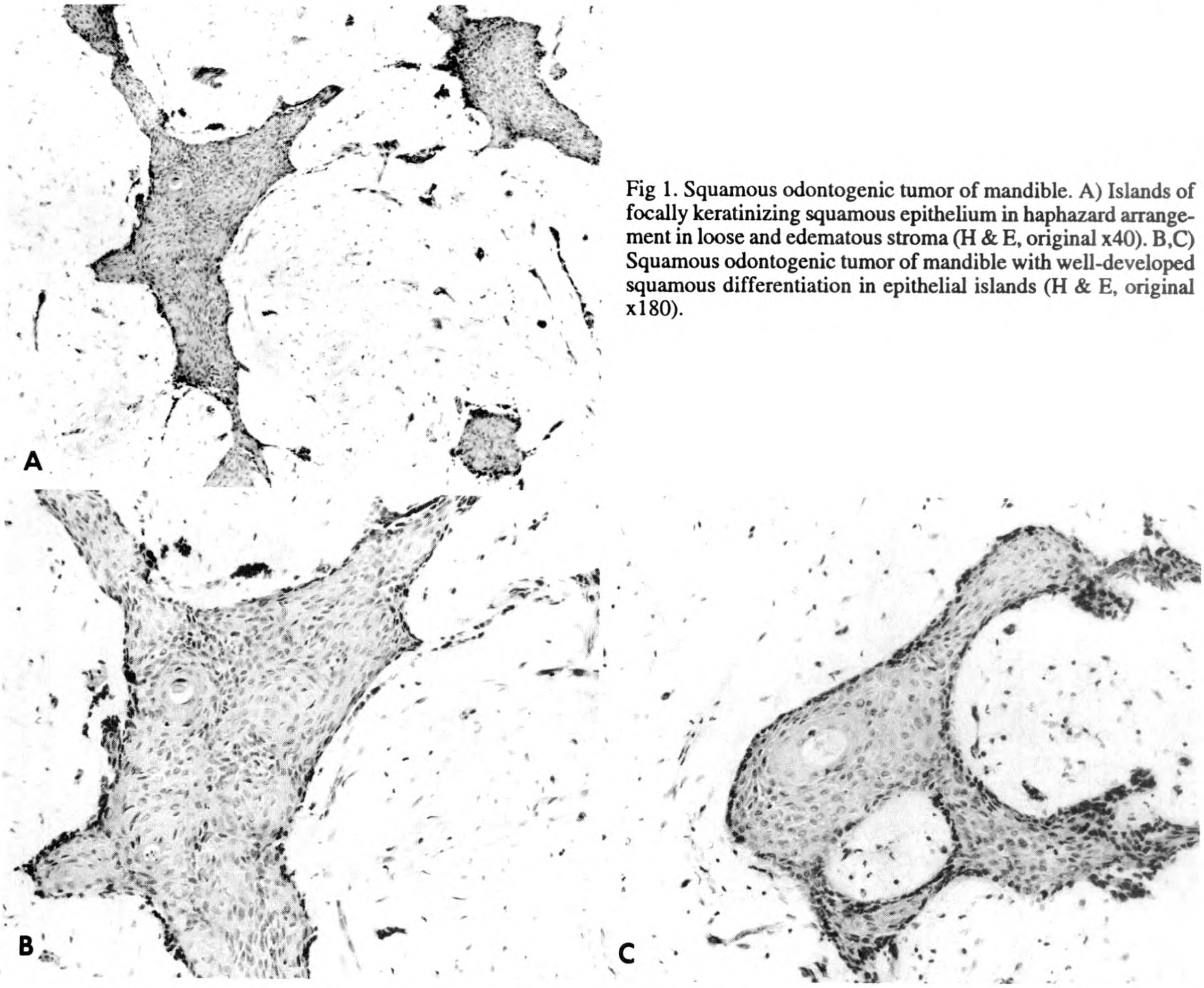

Fig 1. Squamous odontogenic tumor of mandible. A) Islands of focally keratinizing squamous epithelium in haphazard arrangement in loose and edematous stroma (H & E, original x40). B,C) Squamous odontogenic tumor of mandible with well-developed squamous differentiation in epithelial islands (H & E, original x180).

From the Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

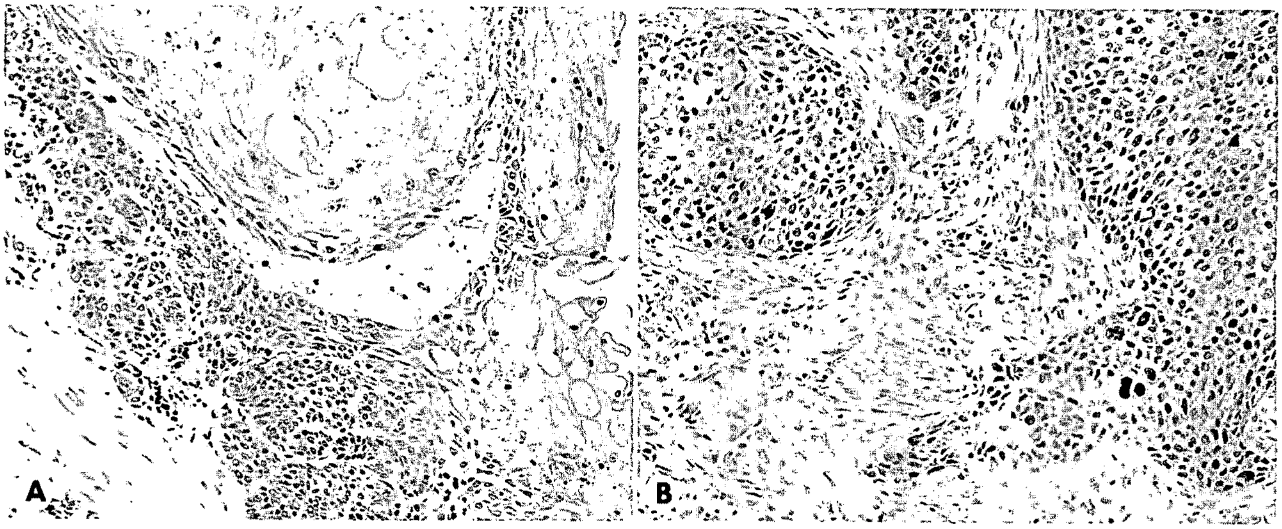

Fig 2. Squamous cell carcinoma. A) Lower left, arising in dentigerous cyst of mandible (H & E, original x200). B) Intraosseous, of mandible (H & E, original x180). Contrast carcinoma's nuclear pleomorphism to differentiated appearance of cells in squamous odontogenic tumor in Fig 1.

first completely extraosseous type in 1993.

The solid, nonmural form of the squamous odontogenic tumor occurs over a wide age range from adolescence to the mid-seventies, with a peak frequency in the third decade.[2,3] There is an almost 2:1 male predilection.

There is nearly an equal distribution of the lesions between the maxilla and the mandible.[1-3] The most common site in the mandible is the premolar-molar region; in the maxilla the incisor-canine region is the area of predilection.[2,3] Multiple sites of involvement are not uncommon (25%).[2] Signs and symptoms associated with the solid squamous odontogenic tumor include mobility of teeth, pain and sensitivity to percussion, and deep pocket formation.[3]

Radiographic findings are quite characteristic and consist of a triangle-shaped or semicircular radiolucency of alveolar bone, with the narrow part of the lesion toward the alveolar crest.[2,3] There may be a scalloped radiodense border at the wider margin of the lesion.[3]

The solid tumor is composed of islands, irregularly disposed and irregularly shaped, of benign squamous epithelium. The islands lack the peripheral polarization of cells seen in ameloblastomas. The islands may be with or without cystic retrogressive changes and central calcification. There is an absence of mitotic activity. The epithelial islands reside in a mature fibrous connective tissue in which there may be a mild chronic inflammatory infiltrate (Fig 1).

The mural variant arising in odontogenic cyst walls shows a slight predilection for the mandible and mostly occurs in patients in their thirties and forties.[2,3] The clinical behavior of this lesion is that of the maternal cyst and does not appear to be modified by the squamous odontogenic tumor component. There is also no evidence that the mural lesions evolve into the solid squamous odontogenic tumor.[3]

The very rare extraosseous variant is believed to arise from overlying gingival epithelium, much like peripheral ameloblastomas.[2]

Squamous odontogenic tumors have usually been successfully managed by local excision, although en bloc resection may be necessary.[1-3] Recurrences are unusual, and none of the reported examples have escaped local control.[2] Maxillary lesions are claimed to be more locally expansive than mandibular lesions.[3] Malignant change has never been described.[2]

The important differential diagnosis is squamous carcinoma in the jaws, either primary intraosseous or metastatic (Fig 2).

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BOOK REVIEWS

Hearing Loss

Robert Thayer Sataloff and Joseph Sataloff. Third edition, revised and expanded. Soft cover, illustrated, indexed, 522 pages, 1993. Marcel Dekker, New York, NY, $69.75.

Both Drs Sataloff are professors at Jefferson Medical College in Philadelphia and, combined, they have authored or coauthored over 300 journal articles or book chapters and 18 books on various aspects of otolaryngology.

A tremendous amount of new knowledge regarding hearing loss has been attained since the first (1966) and second (1980) editions of this book were published. After a foreword by the notable otologist Dr Howard P. House, the authors present the newer information, along with the older, in a well-delineated and easy-to-read composition consisting of 18 chapters.

Appropriately, the prevailing philosophy of the authors is made evident in the first chapter, Hearing Loss: An Overview. From time to time, physicians in all specialties become so involved in the scientific and technical aspects of medicine that they overlook the subtle ramifications of the disease they are treating. It would benefit them and their patients if they would read these 2 brief pages, which, although addressing hearing loss specifically, are applicable to many other conditions. Since an "overview" is generally conceived to be historical in nature, it might be argued that this chapter should have been entitled Hearing Loss: Its Impact, for that is its substance.

In the succeeding chapters, the physics of sound, the anatomy and physiology of the hearing mechanism, the different types of hearing loss and the various causes of them, audiometry, special testing, pediatric hearing loss, treatments, rehabilitation, and other pertinent aspects of managing the hearing loss patient are discussed. The chapters on tinnitus, dizziness, and facial paralysis are new in this edition, and present the most current knowledge of them.

Most experienced physicians have developed their own philosophy and protocol for the diagnosis and treatment of conditions frequently seen in their patients. Little fault can be found with those expressed by these authors. They are consistent with good medical care and devoid of cavalier measures.

To present a text that would be useful to the broad range of caregivers involved in the treatment and management of hearing loss patients, the authors have refrained from using highly technical terms and descriptions. By their nature, however, some topics (such as the physics of sound) will still be difficult for those not intimately involved in that area. Even so, a reasonably educated layman should be able to glean some useful information from them, and those more familiar with the topics will find them to be a good, quick update. The abundant use of self-explanatory graphs, charts, and tables, along with case reports, also aids the reader who seeks pertinent information that can be quickly applied. Although some chapters are followed by a bibliography, the authors have chosen to present a comprehensive list of suggested reading at the end of the book.

Since symptoms, and some are subtle, of hearing loss may be expressed by patients to any health care provider, this is a book that should at least be read by most physicians and rehabilitation therapists. Certainly, those involved in the fields of otorhinolaryngology, general medicine, pediatrics, rehabilitative medicine, geriatrics, genetics, and related areas, including students, interns, and residents, should have it as a readily available reference.

DENNIS G. PAPPAS, MD
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Pediatric Facial Plastic and Reconstructive Surgery

James D. Smith and Robert M. Bumsted, editors. Hard cover, illustrated, indexed, 403 pages, 1993. Raven Press, New York, NY.

In addition to their own expertise, that of 38 colleagues (most representing a broad geographic area of the United States and at least 1 from Canada) is presented by the editors in this text. This statistic is one indication that pediatric facial and reconstructive surgery has become a surgical specialty, and the credentials of the contributors denote that it encompasses the combined skills of a number of health care disciplines.

Although trauma accounts for many facial plastic and reconstructive problems in children, most arise from congenital disorders. Management of these is challenged by the complex anatomy of the head and neck and the juxtaposition of vital organs and structures, which is further punctuated in pediatric cases by their continuing growth. It is pointed out in the text that some of these problems will require a team approach of specialists, and many will require multiple or serial operations.

The opening chapter addresses syndromes and craniofacial disorders. While only a few syndromes are specifically discussed, the authors provide help for the reader to explore new developments in the diagnosis and treatment of these cases. Of the next 24 chapters, 10 cover the topics of congenital anomalies of the nose, ear (otoplasty, congenital auricular abnormalities), eye, and head and neck (masses and vascular lesions). There are 8 chapters on the lip and palate, each emphasizing new treatments. The closing chapters discuss general subjects, such as wound healing, facial nerve abnormalities, dermatologic diseases, anesthesia, recommendations for surgery, and the infrequently discussed psychologic effects and their implications for children who have this type of surgery.

As a rule, great detail in surgical repair is not presented for every procedure; however, the 2 most common techniques are described for some. Perhaps of more significance than the surgery are the discussions of rare and unusual conditions, such as the one on soft tissue sarcoma (rhabdomyosarcoma) in infants and children, which is found in the chapter on malignant and benign tumors of the head and neck. That particular chapter lists 265 references.

In general, the text is well amplified by photographs (some in color) and drawings, and most of the chapters conclude with an adequate bibliography. This is a book that should appeal to many physicians and surgeons dealing with pediatric patients with disorders of the head and neck.

DENNIS G. PAPPAS, MD
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Surgical Anatomy of the Face

Wayne F. Larrabee, Jr, and Kathleen H. Makielski. Hard cover, illustrated, indexed, 213 pages, 1993. Raven Press, New York, NY.

The 2 senior authors and 2 of the 3 contributing authors are from the Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine, in Seattle. The third contributing author is from the neighboring University of British Columbia School of Medicine. It is to their credit that the distinguished head and neck surgeon Dr John Conley endorsed their text with his foreword.

A knowledge of the anatomic structures and landmarks encountered in face lifts, facial reanastomosis, trauma repair, and other facial plastic procedures is essential. The authors successfully and clearly present functional anatomy of the face as it relates to surgical techniques through the use of photographs and graphic illustrations, the latter done extremely well by Dr Makielski.

In 17 chapters, the authors systematically and pragmatically address facial contour analysis; variations in facial anatomy with race, sex, and age; hard-tissue foundation; skin and soft tissue; facial musculature; facial nerve; facial sensory innervation; vascular patterns of the face; lymphatics of the face; hair and scalp; forehead and brow; eyelids, anterior orbit, and lacrimal system; nose; ears; cheeks and neck; lips and chin; and the superficial musculoaponeurotic system (SMAS). The detailed description of the last topic is the high point in the text. As a continuous fibromuscular layer that links the muscles of facial expression, the SMAS "provides a conceptual framework to understand the fascial layers of the face." It divides the subcutaneous fat into 2 layers, and contains fibrous septa that extend through the fat, attach to the overlying dermis, and distribute facial muscle contractions to the skin. The SMAS also maintains a consistent relationship with the major vessels and nerves within each area of the face. An understanding of the SMAS, its functions and relationships, has enabled surgeons to achieve longer-lasting results in facial rejuvenations and anatomic solutions to problems presented by the aging face.

In an easily read and understandable text augmented by photographs and the excellent illustrations of Dr Makielski, this book should be found useful by surgeons performing facial plastic procedures, as well as those still in the process of studying them.

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Acoustic Neuroma

M. Tos and J. Thomsen, editors. Hard cover, illustrated, indexed, 1,002 pages, 1992. Kugler Publications, New York, NY, $280.

This new book comprises presentations by almost all of those who participated in the First International Conference on Acoustic Neuroma, which was held in Copenhagen in August 1991. The main purpose of the conference was to bring together a variety of the top-ranking world authorities on basic and clinical research in acoustic neuroma to present their scientific efforts and to convey a common language with which the various problems and results related to this condition can be discussed. Included are the works of otologists, neurosurgeons, radiotherapists, and other researchers.

Twenty-six main subjects with several subdivisions comprise the contents of this book. Every aspect of an acoustic neuroma is covered, although laser application is barely discussed. As is the case in most books of this type, the authors presume the reader to have certain knowledge of the fundamentals of the field. They do not describe the "how to" of each surgical approach in detail, but compare the indications for and the results of each surgical approach to an acoustic neuroma. Clearly shown is that there are specific approaches to meet the needs of the patient. That is to say, the translabyrinthine approach for the patient with poor hearing, or the middle fossa or suboccipital approaches (depending on tumor size) to preserve hearing. At times, there may be no surgical treatment necessary at all, only careful observation. Yet the book concludes that the choice of approach usually depends on the experience of each surgeon. The challenge should, instead, be to tailor the approach to the patient's particular needs and not to the surgeon's bias. This discrepancy is one of the various important topics presented at the end of the book, which is one of the strongest features of the book. Other important topics include a synopsis on diagnoses, measurement of tumor size and classification of tumors, natural history, timing of surgery, hearing preservation, facial nerve sequelae, and near-total and subtotal removal of tumors and of bilateral acoustic neuromas.

Especially emphasized is the concept of a team approach involving different specialties in attempting better management and results. A gamma knife update is needed; otherwise, the book represents the state of the art in acoustic neuroma pathology, diagnosis, and treatment, and will probably be timely for the coming years.

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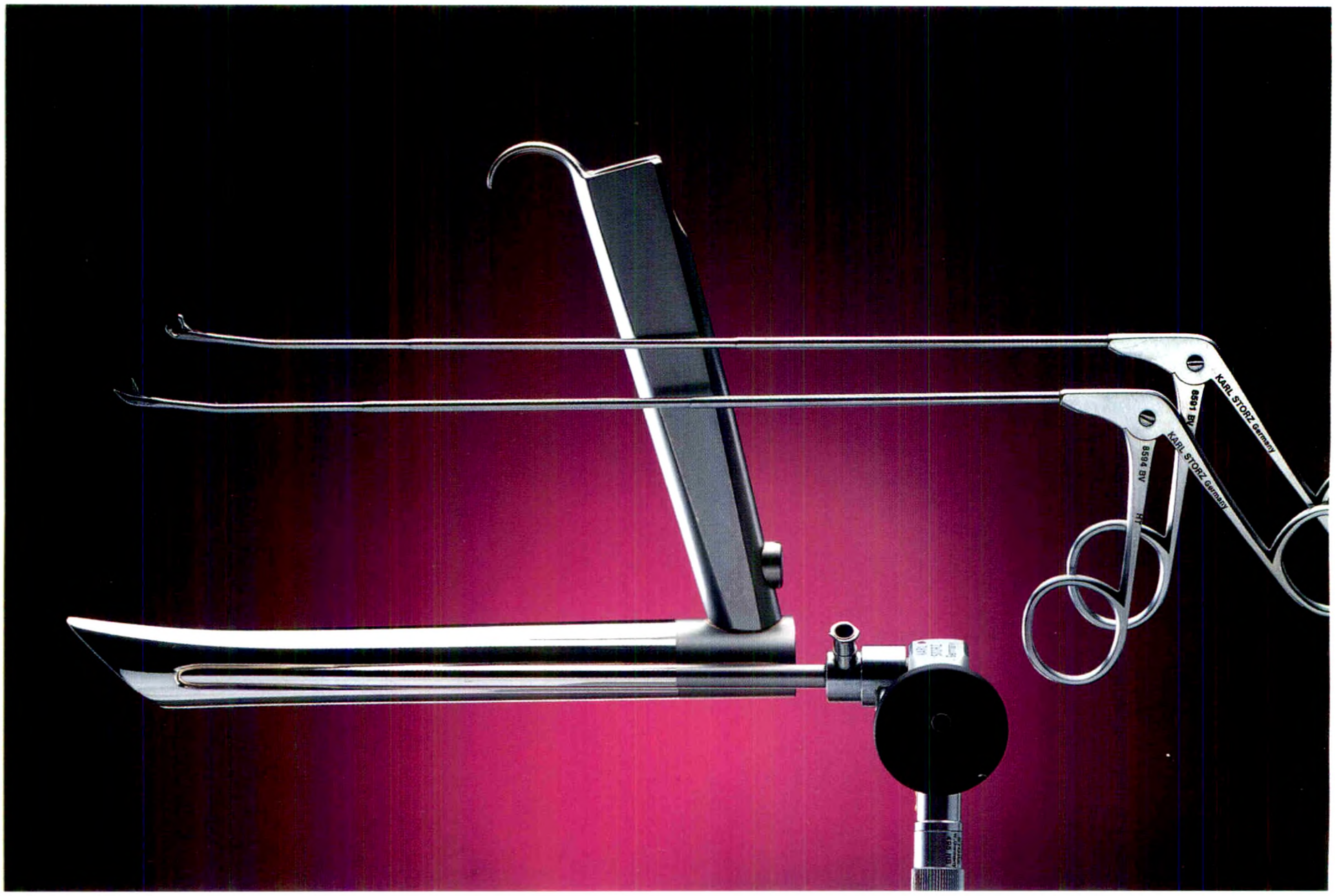

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REPAIR OF A LARYNGOTRACHEOESOPHAGEAL CLEFT IN AN INFANT BY MEANS OF EXTRACORPOREAL MEMBRANE OXYGENATION

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Few survivors have been reported following attempted repair of laryngotracheoesophageal clefts (LTECs). The major challenge is maintaining oxygenation, both during the surgical repair and during the postoperative period of healing. We report a neonate with an LTEC extending to the carina whose successful repair was facilitated by extracorporeal membrane oxygenation (ECMO) begun intraoperatively and continued postoperatively for 11 days. The intraoperative surgical exposure of the defect was excellent. Postoperative trauma to the fresh tracheal repair from ventilatory pressures and endotracheal tube motion was eliminated through the use of ECMO. The patient was discharged without a tracheotomy and with a normal voice, cry, and swallow. According to this result, the use of ECMO may represent a significant advance in facilitating the correction of major laryngotracheoesophageal anomalies. The rationale, advantages, disadvantages, and potential pitfalls of this approach are presented, as well as preoperative and postoperative documentation of our results.

KEY WORDS — cleft larynx, congenital laryngotracheoesophageal cleft, extracorporeal membrane oxygenation.

INTRODUCTION

Laryngotracheoesophageal cleft (LTEC) is a rare congenital anomaly characterized by a midline defect of variable length between the posterior larynx and trachea and the anterior wall of the esophagus. The defect presumably occurs at approximately 35 days' gestation, when there is failure of caudal-rostral advancement of the mesenchymal tracheoesophageal septum, and lack of dorsal fusion of the cricoid cartilages and interarytenoid tissues.[1] Patients often present with increased oral secretions (presumably secondary to a swallowing defect); aphonia or a hoarse cry; coughing, choking, or cyanosis associated with aspiration while feeding; and stridor. Diagnosis is confirmed by laryngoscopy and endoscopy. This report describes the unique management of a patient with an LTEC involving the entire trachea to the level of the carina. Extracorporeal membrane oxygenation (ECMO) was used to facilitate surgical exposure of the defect and for postoperative respiratory support to avoid trauma to fragile tracheal suture lines.

CASE REPORT

A 2,586-g female infant was born at term gestation by elective repeat cesarean section to a 23-year-old gravida 4 para 3-4 mother. The pregnancy was remarkable for polyhydramnios. The infant's Apgar scores were 8 at 1 minute and 9 at 5 minutes.

Shortly after birth, the patient developed respiratory distress that was treated with oxygen. A chest radiograph suggested intrapleural fluid. Over the next 16 hours the patient's respiratory distress worsened and endotracheal intubation was required. Initially, a 3.0-mm–inside diameter oral endotracheal tube was inserted. A loud audible leak with positive pressure ventilation prompted replacement with a 3.5-mm–inside diameter tube. The leak persisted, but with use of a ventilator (fraction of inspired oxygen 0.50, rate 30 breaths per minute, peak inspiratory pressure 20 cm H_2O, positive end inspiratory pressure 3 cm H_2O) the patient clinically improved and hemoglobin oxygen saturations increased from 90% to 100%. She was transferred to our institution for further evaluation and treatment. By 24 hours of age her improving respiratory status allowed extubation. The day following extubation the first oral feeding resulted in gagging and choking. At that time her cry was noted to be hoarse and high-pitched. The following day the patient underwent laryngoscopy, bronchoscopy, and esophagoscopy under general anesthesia while breathing spontaneously. An LTEC extending to the carina was present (Fig 1).

Over the next 2 weeks, the patient remained stable,

From the Departments of Anesthesiology (Geiduschek, O'Rourke), Otolaryngology–Head and Neck Surgery (Inglis, Kozak), Pediatrics (O'Rourke, Mayock), and Surgery (Sawin), University of Washington School of Medicine and Children's Hospital and Medical Center, Seattle, Washington.

Presented at the meeting of the American Broncho-Esophagological Association, Los Angeles, California, April 19-20, 1993.

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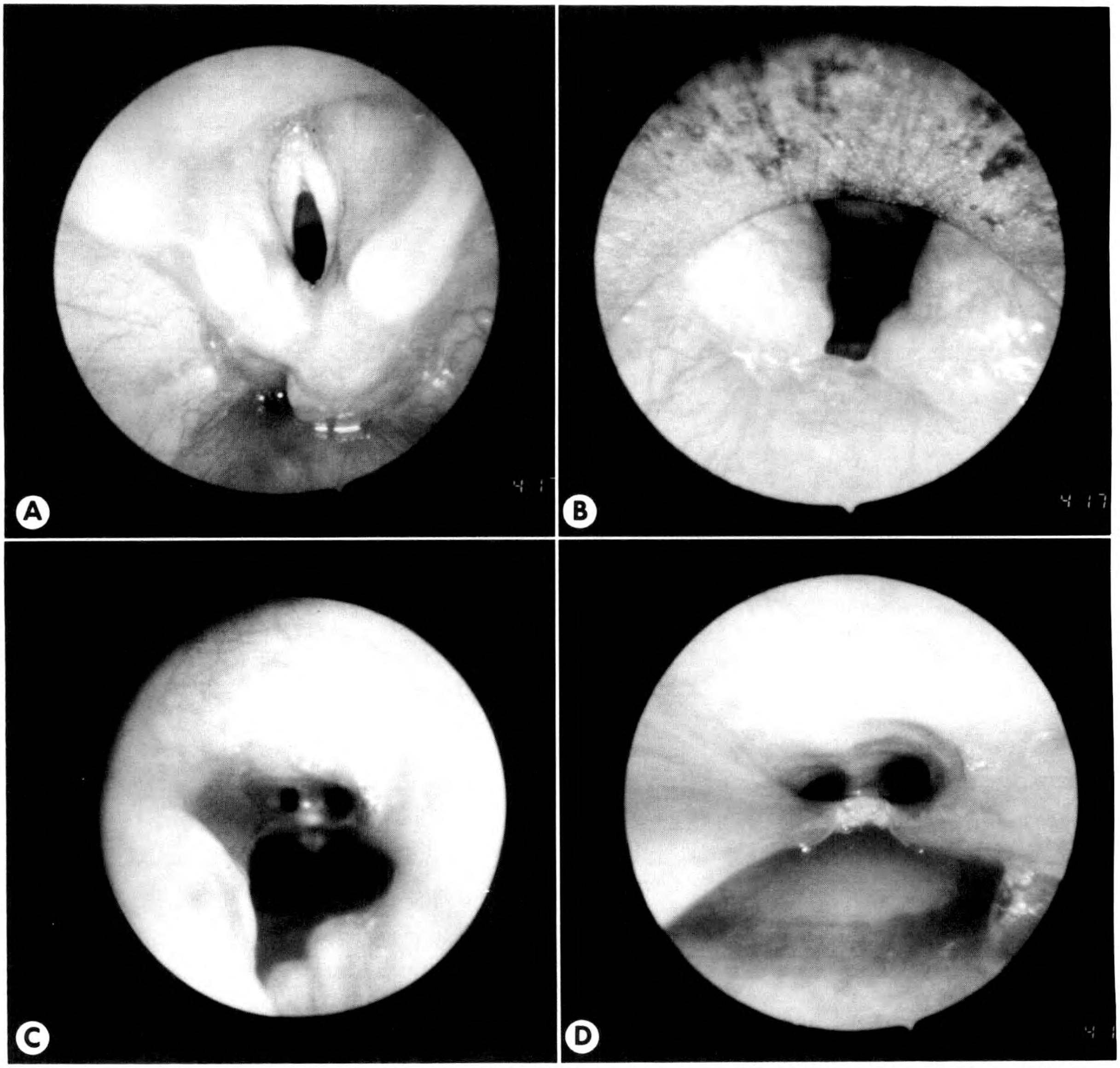

Fig 1. Preoperative views of larynx. A) Interarytenoid portion of cleft is suggested by arytenoidal asymmetry in postcricoid region. B) Cricoid portion of cleft is clearly demonstrated by distracting arytenoids with bronchoscope. C) With telescope positioned just below vocal cords, subglottic portions of arytenoids are visible in lower foreground. Note also tracheoesophageal "shelves," esophagus, carina, and bronchi. D) Gastroesophageal reflux as viewed from midtracheal level.

with hemoglobin oxygen saturations over 94%, while receiving oxygen delivered by nasal cannulae. Nutritional support was with formula administered through a soft nasojejunal feeding tube. Oral secretions were controlled with glycopyrrolate. There were no episodes of aspiration during this period. Cranial ultrasound, renal ultrasound, and echocardiogram findings were all normal. During this period, family members decided to proceed with surgical intervention.

Following induction of general anesthesia with halothane and oxygen, a 4.5-mm endotracheal tube was passed through the esophageal inlet. Fiberoptic bronchoscopy through the tube documented tip placement within the common tracheoesophageal lumen just superior to the carina. The patient was then positioned and prepared for ECMO cannulation. The common carotid artery and internal jugular vein were isolated through a transverse incision in the right supraclavicular fossa. The patient was anticoagulated with heparin sodium and the vessels were cannulated. To decrease bleeding a loading dose of aminocaproic acid, 100 mg/kg, was administered intravenously, followed by an infusion administered at 30 mg/kg per hour for the first 4 postoperative days. Extracorporeal membrane oxygenation was initiated and the cannulae positions were optimized with the aid of transthoracic echocardiography. The patient was then positioned for repair of the cleft with the head midline and neck

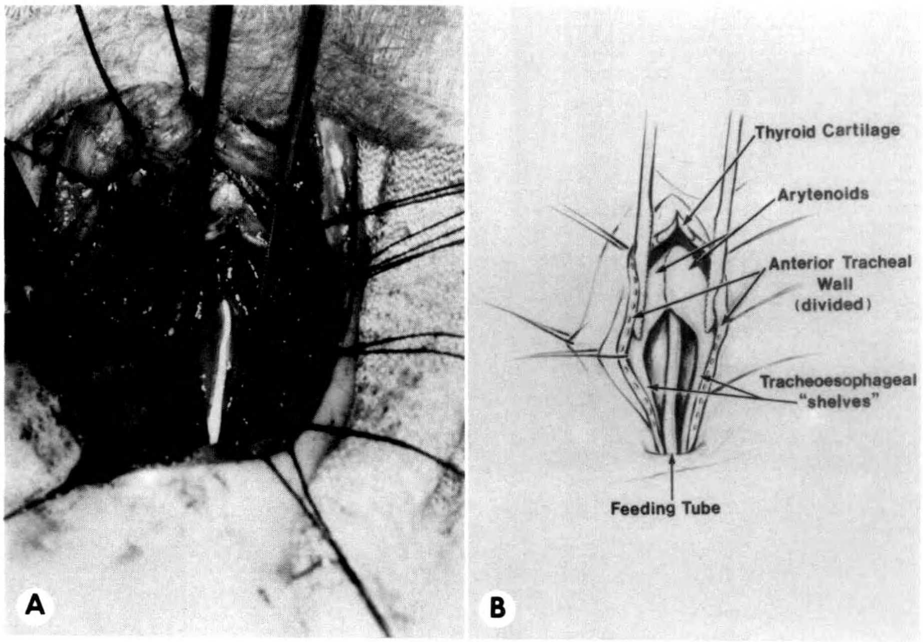

Fig 2. Following division of anterior tracheal wall and removal of esophagotracheal tube. Cannulae are visible but in no way interfere with operative exposure. A) Intraoperative photograph. B) Artist's depiction of photograph.

maximally extended. Again, ECMO cannulae position was reevaluated with echocardiography. Because of the extreme hyperextension of the neck required for tracheal exposure, the cannulae had to be repositioned more inferiorly during this portion of the procedure.

The entire laryngotracheal complex to the carina could be visualized through a low apron flap incision. The trachea, cricoid cartilage, and lower thyroid cartilage were divided vertically in the anterior midline, exposing the cleft. The esophagotracheal tube was removed (Fig 2). The nasojejunal feeding tube remained in situ. A neoesophagus and posterior wall of the trachea were created by means of mucosal flaps dissected from the lateral walls of the cleft (Fig 3). A 2.5-mm–inside diameter nasotracheal tube was placed by the anesthesiologist and positioned by the surgeon under direct vision above the carina prior to closure of the anterior trachea and larynx. Estimated blood loss was less than 10 mL, despite the heparinization.

The patient was transferred to the intensive care unit while on ECMO. No positive pressure ventilation, positive end expiratory pressure, or oxygen was administered via the endotracheal tube. Neuromuscular blockade was not maintained during the postoperative ECMO course, and the patient made breathing efforts during this time with minimal audible air entry into the chest. Nasotracheal suctioning was permitted only within the lumen of the endotracheal tube. Daily chest radiographs revealed complete opacification of both lung fields. Morphine sulfate (20 to 40 μg/kg per hour), midazolam hydrochloride (50 μg/kg per hour), and lorazepam (50 μg/kg every 4 hours as needed) were administered intravenously

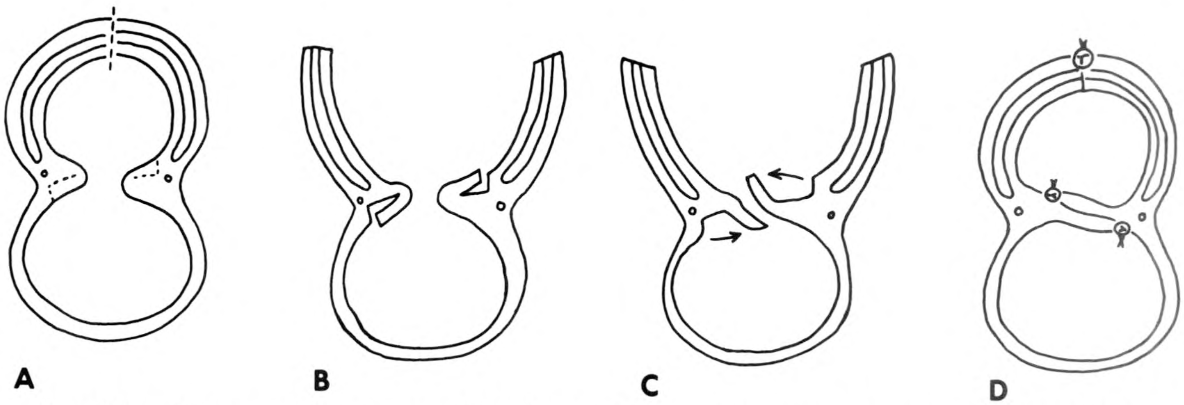

Fig 3. Schematic representation of mucosal flaps developed from tracheoesophageal "shelves." A) Site of anterior tracheal incision and proposed mucosal flaps. B) Anterior tracheal wall has been divided and mucosal flaps for tracheoesophageal wall have been created. C) Flaps are rotated into position. D) Representation of 2-layer closure of tracheoesophageal wall and 1-layer closure of anterior tracheal wall.

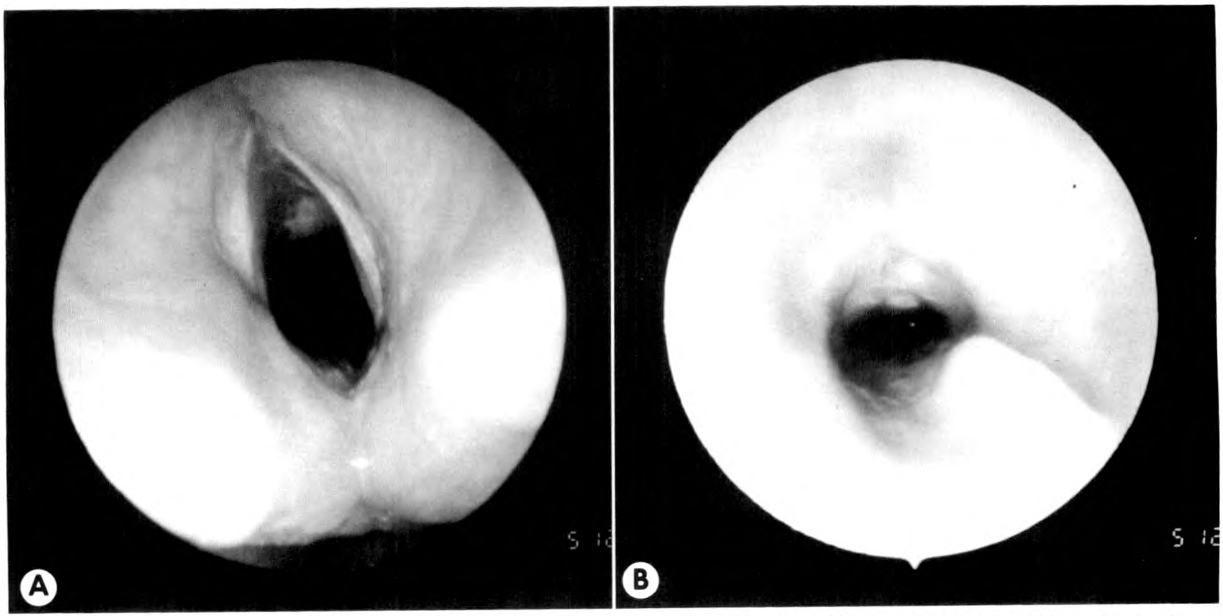

Fig 4. Immediate postextubation views. A) Larynx. Gentle distraction of arytenoids revealed good mucosal closure in interarytenoid region. B) Trachea. Complete closure of cleft is evident. Over ensuing months, patient developed moderate tracheomalacia, which is not apparent here.

for sedation and comfort. There was no gastric drainage tube. Neither gastric distention nor accumulation of oral secretions occurred. Ranitidine hydrochloride prevented acid reflux on the fresh esophageal suture line.

In the first 12 postoperative hours there was 50 mL of blood loss through the cervical drain; this volume was replaced with packed red blood cells. On the first postoperative day the venous ECMO cannula tip was documented to lie in the right ventricle by chest radiography and transthoracic echocardiography. The lateral neck incision was opened and the cannula tip repositioned. Catheter migration was most likely a result of changing head position following the operation.

We arbitrarily allowed 7 days for the suture lines to heal prior to attempting to reexpand the lung with positive pressure ventilation. Attempted fiberoptic bronchoscopic inspection of the suture lines was unsuccessful because of inspissated tracheal secretions. Subsequently, rigid bronchoscopy revealed an intact suture line. A 3.0-mm–inside diameter endotracheal tube replaced the 2.5-mm tube, and mechanical lung ventilation and gentle percussion chest physiotherapy were instituted. Areas of atelectasis persisted on chest radiographs, and a large audible air leak was present around the endotracheal tube at low peak inspiratory pressures. On postoperative day 10, rigid bronchoscopy revealed tracheal secretions but no area of tracheal collapse. A 3.5-mm–inside diameter endotracheal tube was placed. Over the next 24 hours the patient received repeated courses of chest physiotherapy and endotracheal suctioning. Chest wall compliance, breath sounds, and chest radiographs improved. The patient was successfully weaned from ECMO and decannulated on the 11th postoperative day.

On the 14th postoperative day, the patient was brought to the operating room. A halothane and oxygen anesthetic was administered via the endotracheal tube with the patient breathing spontaneously. She was extubated and rigid esophagobronchoscopy revealed well-healed suture lines and minimal tracheomalacia (Fig 4). She emerged from anesthesia without reintubation. She had no respiratory distress and no accumulation of oral secretions. On the 16th postoperative day, a videofluoroscopic swallowing evaluation demonstrated a normal oral and pharyngeal phase with microaspiration from gastroesophageal reflux. The next day thickened oral feedings were started with the patient supported in a feeding wedge. Initially, oral feeding constituted only 25% of the patient's necessary caloric requirement, the remainder being provided by parenteral hyperalimentation.

On the 22nd postoperative day, group D streptococcal sepsis required treatment with a 10-day course of ceftriaxone sodium and gentamicin sulfate. The patient recovered uneventfully.

Postprandial emesis occurred regularly. An upper gastrointestinal series on the 28th postoperative day demonstrated decreased lower esophageal motility, gastroesophageal reflux, and delayed gastric emptying. Pyloric thickening consistent with a diagnosis of pyloric stenosis was seen on abdominal ultrasound. On the 31st postoperative day, the patient underwent pyloromyotomy and placement of a gastrostomy button. Intravenous metoclopramide hydrochloride and continuous drip feedings via gastrostomy were started on the 33rd postoperative day. On the 38th postoperative day, oral feedings were started. On the 50th postoperative day the patient was discharged.

Over the following 10 months the patient demonstrated some weight gain and linear growth, but remained below the fifth percentile for her age in height and weight. Her caloric needs were considered to be above normal because of the increased work of breathing secondary to her collapsing trachea. As a result, supplemental feedings via gastrostomy were instituted. Gastroesophageal reflux persisted and she underwent a Nissen fundoplication at 10 months of age. The patient is currently 18 months old and is having improved weight gain. There currently are no immediate plans regarding further intervention to manage her tracheomalacia.

DISCUSSION

To our knowledge, this case represents the first time ECMO has been used to facilitate repair of an LTEC.

There are several anatomic classification schemata for laryngeal clefts.[2-5] Benjamin and Inglis[6] proposed 4 categories of clefts. Type 1 is a supraglottic interarytenoid cleft. Type 2 clefts involve extension into but not through the posterior lamina of the cricoid cartilage. Types 1 and 2 are minor clefts, usually not requiring tracheostomy, and may be either managed conservatively or if necessary repaired endoscopically. Type 3 clefts extend through the cricoid cartilage and may involve the cervical trachea. Type 4 clefts extend below the thoracic inlet. All types of clefts may be associated with other congenital anomalies that may affect morbidity and mortality.[7,8] Type 4 clefts have a particularly poor prognosis, with only 3 survivors previously reported.[9-11] Two of these patients required tracheostomy as part of their repair.[9,10]

Because the patient did not have any other congenital anomalies that would affect outcome, we did offer the possibility of repair to the family. Their decision to intervene was made with difficulty. They were aware of the potential for fatal outcome or serious permanent morbidity if repair was attempted and also were aware of the eventual occurrence of fatal pulmonary aspiration if no repair was attempted. The decision to use ECMO for the repair was based on our knowledge of the poor survival with such a major defect (types 3 and 4) with the described methods of conventional anesthesia and postoperative ventilation.

Airway management during these operations is cumbersome. Stabilizing the airway has been accomplished with a tracheostomy, endobronchial intubation, or placement of an endotracheal tube in the residual stub of the distal trachea (nonexistent in this case).[12-15] Donahoe and Gee[9] and Ryan et al[10] have utilized custom-made bifurcated endotracheal tubes with each lumen entering a main stem bronchus. All of these methods interfere with access to the surgical site. The use of ECMO in this case obviated the need for an endotracheal tube and maximized exposure of the operative field.

A goal of this patient's perioperative management was to avoid positive pressure ventilation prior to institution of ECMO. The presence of a common tracheoesophagus theoretically would make positive pressure ventilation problematic, with the majority of each breath inflating the stomach or leaking around the endotracheal tube. Fortunately, gas exchange was supported with spontaneous ventilation during this phase of the procedure. If the patient had required ventilatory assistance, we were prepared to deliver positive pressure ventilation through a rigid bronchoscope (with side holes obliterated) into 1 of the main stem bronchi. Alternatively, an inflatable balloon-tipped catheter (eg, Foley) could have been passed into the stomach, with the inflated balloon occluding the gastroesophageal junction.[16]

Recurrent laryngeal clefts requiring reoperation occur in 11% of reported cases,[17] so we performed several postoperative measures to reduce trauma to the fresh suture lines. Trauma to the esophageal side of the repair was minimized by not placing a nasogastric tube and by maintaining the patient on an H_2 receptor histamine antagonist to prevent acid reflux. The soft silicone nasojejunal feeding tube that was inserted early in the patient's hospital course remained in situ following repair. This tube was considered to be of small enough caliber and soft enough consistency to not cause pressure necrosis to the esophageal side of the repair. Trauma to the tracheal side of the repair was minimized by maintaining ECMO postoperatively, eliminating both the barotrauma of positive pressure ventilation and the mechanical trauma to the posterior tracheal wall that would have been produced by the necessarily larger endotracheal tube. The small endotracheal tube that was left in place at the completion of the procedure allowed for suctioning, but would have been used for ventilation only if emergency separation from ECMO was required (eg, because of ruptured tubing, air embolism, or acute oxygenator failure).

While ECMO provided the advantage of avoiding positive pressure ventilation, we recognized its many risks. The greatest potential risk of ECMO is hemorrhage, with central nervous system hemorrhage potentially the most devastating. In any surgical patient receiving ECMO, there is the added risk of bleeding at the surgical site. Other complications associated with ECMO include technical difficulties with cannulation or the circuitry, air or particulate matter embolization, hemolysis, transfusion-associated infections, and possible subtle, long-term neurodevelopmental sequelae.[18] However, since neurologic outcome following ECMO has been evaluated in patients who were also critically ill from cardiorespiratory disease, it is difficult to discern exactly what added risks ECMO posed for our patient.

Compared to our usual ECMO protocol for treating neonates with severe, persistent pulmonary hypertension, several things were done differently with this patient regarding hemostasis: the heparin infusion was adjusted to maintain an activated clotting time of 180 to 200 seconds, compared to a range of 220 to 240 seconds in the nonsurgical patient; platelets were transfused whenever the platelet count dropped below 110,000/mm^3, as opposed to 80,000/mm^3 in other patients; and aminocaproic acid was used to reduce the postoperative hemorrhage associated with chronic heparinization while on ECMO.[19] Hemorrhage during the surgical procedure was minimal. Following the episode of hemorrhage through the cervical drain, there was minimal bleeding from the surgical sites.

Transthoracic echocardiography for determining ECMO cannulae positions has been very helpful in our practice by providing real-time assessment while cannulae are repositioned as needed. This optimizes venous return to the ECMO circuit. Subsequently, ECMO flow rates can be maximized and lower activated clotting times tolerated. The higher flow rates decrease the amount of clot formation in the ECMO circuit and therefore the risk of embolization to the patient. An unanticipated difficulty was the need to reposition the cannulae following the placement of the neck in extreme extension for cleft repair, and again when the neck was placed back in the neutral position postoperatively. The need to reposition the cannulae could possibly have been avoided by initially placing the cannulae in the lowest acceptable position.

We considered cardiopulmonary bypass as an alternative to ECMO for intraoperative management. We are not aware of a reported case in which it has been tried. The major advantages to considering the use of cardiopulmonary bypass are its availability at most major medical centers and that its use does not require sacrificing a carotid artery. However, cardiopulmonary bypass cannot be maintained longer than several hours. We opted for the use of ECMO in order to provide several days of ventilatory support and to avoid trauma to the fresh repair.

In summary, we have presented a case report of an infant undergoing repair for an LTEC with ECMO support. Extracorporeal membrane oxygenation provided improved surgical exposure and potentially minimized postoperative tracheal trauma. It must still be considered a high-risk procedure, but given the overall poor survival for infants with this defect, we would recommend that a similar approach to repair involving the use of ECMO be considered in the future.

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TRACHEOSCOPE: AN OLD INSTRUMENT WITH NEW APPLICATIONS

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The tracheoscope is a bronchoscope without the side ventilating ports at the distal tip. It has been used for decades, implementing diagnostic and therapeutic procedures in the subglottis and cervical and thoracic trachea. The closed tube tracheoscope allows excellent control of the airway with maintenance of continuous anesthesia and ventilation. Flexible fiber–directed lasers, such as the potassium-titanyl phosphate laser, can be used with the tracheoscope for laser resection or vaporization of diseased tissue from just below the vocal cords to any level within the trachea. Controlled anesthesia and smoke evacuation are maintained throughout the operation, allowing a relatively safe endoscopic procedure. Disorders such as subglottic hemangioma, subglottic or tracheal webs, papillomatosis, granuloma, and a variety of neoplastic growths can be excised, debulked, or submitted to biopsy by means of this instrument. In the neonatal and infant airway, use of the tracheoscope concomitantly with rigid telescopes has been particularly rewarding.

KEY WORDS — bronchoscope, laser, tracheoscope.

The tracheoscope has been available for generations, but it is now used so infrequently that many otolaryngologists are unaware of its benefits, particularly in children. It is obvious from manufacturing companies' sales of this instrument that very few medical centers even possess these valuable pieces of equipment.

Many excellent techniques are available for examining and diagnosing subglottic and tracheal disorders. However, when endoscopic therapeutic procedures are required, the options for surgical care and instrument selection diminish rapidly. Endoscopic surgical manipulation in the subglottis and cervical trachea can be difficult, challenging, and hazardous.

Instruments such as the Healy subglottiscope[1] were specifically designed to achieve optimal surgical results just below the vocal cords. While it is an excellent tool, 2 limitations of this instrument are that it will not extend very far into the cervical trachea and that it requires an open anesthesia technique. The "open" anesthesia technique refers to an available access through the instrument, so that positive end expiratory pressure is not possible; stated more simply, there is a big air leak. The bronchoscope is the time-honored piece of equipment for working in the lower trachea and bronchi, and it provides a closed system technique for anesthesia. The bronchoscope also has limitations in that the side ventilating ports severely hamper its use in the subglottis and upper trachea, as these ports allow a massive air leak in the hypopharynx, and ventilation of the patient is not

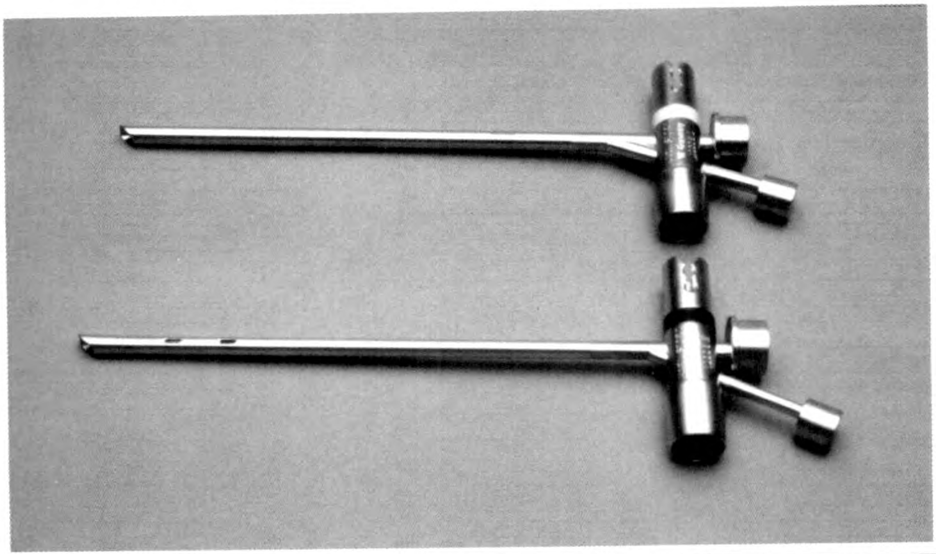

Fig 1. Tracheoscope and bronchoscope are identical except for side ventilating ports on distal shaft.

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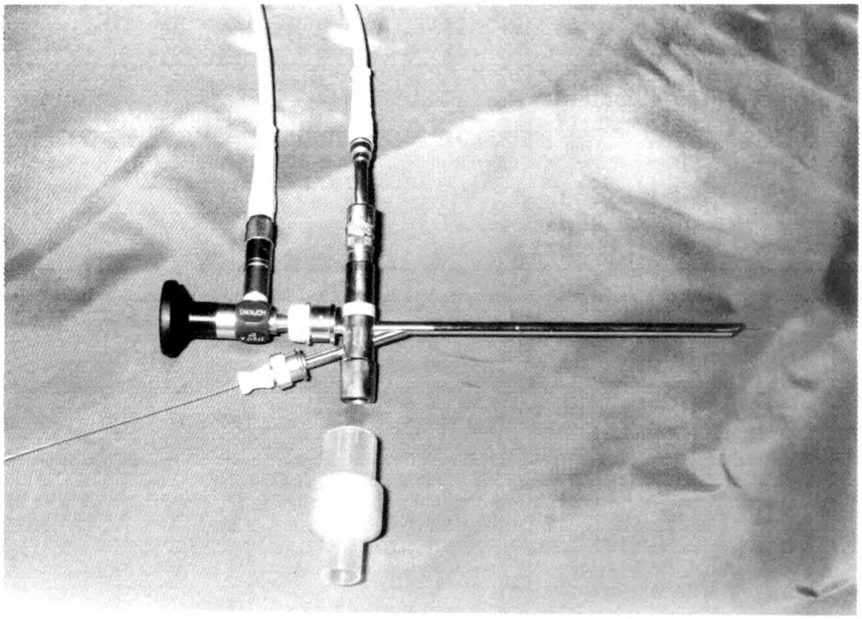

Fig 2. Flexible laser fiber is advanced through side channel and lies beside telescope. Distal tip is only 6 to 10 mm in front of telescopic lens.

adequate.

The tracheoscope is simply a bronchoscope without the side ventilating ports (Fig 1). It is well described in the adult literature.[2-6] As soon as the tip of the instrument is placed through the glottis, a closed anesthetic system is secured and complete airway control is available, satisfying both the anesthesiologist and the endoscopic surgeon.[7] This is a very safe airway. The instrument can then be utilized from the superior subglottis to the carina with no time constraints for either diagnostic evaluations or therapeutic manipulations. Tracheoscopes are available through such instrument companies as Karl Storz, Pilling, and Wolf in various sizes, from an infantile 2.5 to the large adult 9.0.

Flexible fiber lasers, such as the potassium-titanyl phosphate (KTP/532) laser, can be used with the tracheoscope by passing the laser fiber down the side channel and keeping the anesthesia technique closed (Fig 2). A telescope can be used simultaneously, providing optimal visualization for precise endoscopic work. A flexible suction instrument can also be passed down the same side channel with the laser fiber for smoke evacuation, but this is rarely necessary. This arrangement with the telescope and laser fiber is good for such problems as soft subglottic webs or scars, recurrent respiratory papillomatosis, subglottic hemangioma with tracheal extension, tracheotomy stoma granulomas (either for decannulation or whenever the lesions are obstructive), and benign tracheal neoplasms.

Flexible endoscopic alligator clamps or biopsy forceps can also be advanced through the side channel to remove small foreign bodies or tissue (Fig 3). The 1.9-mm telescope can be passed in a 2.5 tracheoscope after the tip of the flexible instrument is introduced ahead of the telescope. This allows very precise manipulation of even the smallest mass in an infantile airway.

During evaluation of tracheomalacia, as the bronchoscope or tracheoscope is advanced into the airway, the round distal tip of the instrument will dilate the collapsing airway. If no telescope is used, the diagnosis easily can be missed. Even when a telescope is used, if it is only the same length as the bronchoscope or tracheoscope, the dilation caused by the advancing round sheath can still mask the anomaly. For that reason, a telescope that is at least 4 cm longer than the bronchoscope or tracheoscope is recommended. When a tracheoscope is used, the distal tip can be placed through the vocal cords, securing the airway. The small-diameter telescope can be advanced well ahead of the tracheoscope, preventing dilation and making the diagnosis of a collapsing airway more obvious to the surgeon. A bronchoscope with its side ventilating ports would have a massive air leak above the vocal cords during subglottic or cervical tracheal examinations.

The tracheoscope is limited to use in the subglottis and trachea in normal conditions. It should not be advanced into main stem bronchi, either for examination or for surgical manipulation, as the opposite lung will not be ventilated.

Experience with the tracheoscope has shown that it is useful for a wide variety of ages and conditions. This relatively inexpensive tool broadens the types of diagnostic and surgical procedures available to the endoscopic surgeon.

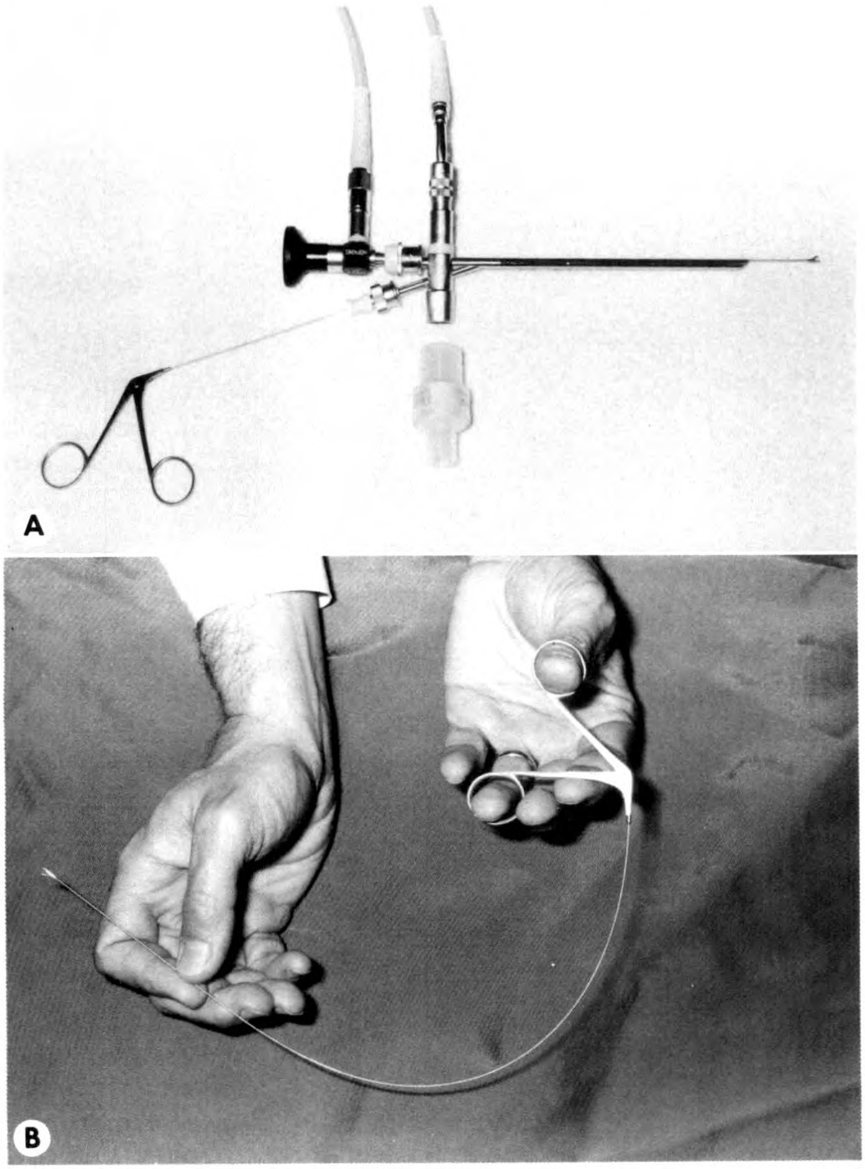

Fig 3. A) Flexible endoscopic microinstruments can also be placed through side channel, and shaft lies beside telescope. B) These instruments are highly flexible to allow passage even in small tracheoscopes.

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PHRENIC NERVE REINNERVATION OF THE CAT'S LARYNX: A NEW TECHNIQUE WITH PROVEN SUCCESS

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Reinnervation of the posterior cricoarytenoid muscle (PCA) should provide vocal cord abduction on inspiration, and passive adduction to enable phonation. Previous investigators have shown that reinnervation is possible, but results have not been clinically encouraging. When reinnervation was successful, the question remained whether it was provided by the transplanted nerve or by the ingrowth of adjacent nerves. In this study the phrenic nerve was transplanted directly into the PCA in a series of 12 cats. Fibrin glue was used to overcome nerve trauma and to prevent retraction of the nerve from the PCA. Laryngoscopy, electromyography, and retrograde labeling of the phrenic motoneurons provided evidence of functional reinnervation in 9 cats. Partial or complete failure in the remaining 3 was due to retraction of the nerve from the muscle. These results appear to justify trials of the procedure in humans.

KEY WORDS — laryngeal paralysis, phrenic nerve, reinnervation.

INTRODUCTION

Vocal cord lateralization procedures successfully relieve the inspiratory stridor produced by bilateral abductor laryngeal paralysis. Unfortunately, this procedure may result in significant deterioration in voice quality, aspiration of liquids, and ineffectiveness of cough. Extensive research aimed at developing a satisfactory technique for reinnervation of the larynx has not provided consistently successful results in the clinical setting.[1] This study was designed to develop a relatively simple and reliable technique for restoring physiologic vocal cord abduction on inspiration, followed by passive return of the cord to the midline during phonation and swallowing. We chose to attempt reinnervation of the posterior cricoarytenoid (PCA) muscle with the phrenic nerve and to prove that the reinnervation was provided by the phrenic nerve. The phrenic nerve is a homogeneous composition of neurons with electrical activity similar to that recorded in the normally innervated PCA muscle. Electrical activity in the phrenic nerve and the recurrent laryngeal nerve is increased with inspiration and decreased with coughing and phonation.[1] Fackler et al[2] delineated the effects of unilateral phrenic nerve section and demonstrated little effect on ventilatory capacity 6 months postoperatively. In 1924, Ballance[3] attempted anastomosis of the phrenic nerve to the recurrent laryngeal nerve. Since then, others have attempted to improve on his technique with limited success, encountering unreliable innervation and synkinesis.[4-10] In order to overcome these problems, the phrenic nerve was implanted directly into the denervated PCA muscle. Heterotypic innervation of this type has been successful in other systems and can be confirmed morphologically by retrograde labeling of the motoneurons supplying the treated muscle.

Horseradish peroxidase is a proven neural labeling substance.[11] This enzyme is taken up by viable exposed axons and actively transported retrogradely to be concentrated into the neuron's soma. With appropriate enzymatic reaction, the end product is visualized as a cytoplasmic deposit. This technique was used to identify the source of reinnervation of the PCA muscle (ie, in the phrenic nucleus, in cervical spine segments C-4 to C-6).[11] To minimize potential nerve injury, fibrin glue was used to secure the nerve within the muscle. The use of fibrin glue (Tisseel) is well established as an effective alternative to nerve suture anastomosis.[12,13]

METHODS AND MATERIALS

The results presented here are based on experiments with 12 healthy cats weighing between 2 and 3.5 kg. The experiment proceeded in 5 stages.

1. Section of the left recurrent laryngeal nerve and implantation of the left phrenic nerve in the PCA muscle.
2. Direct laryngoscopy to confirm vocal cord paralysis.
3. Direct laryngoscopy to assess reinnervation (4 to 8 months).

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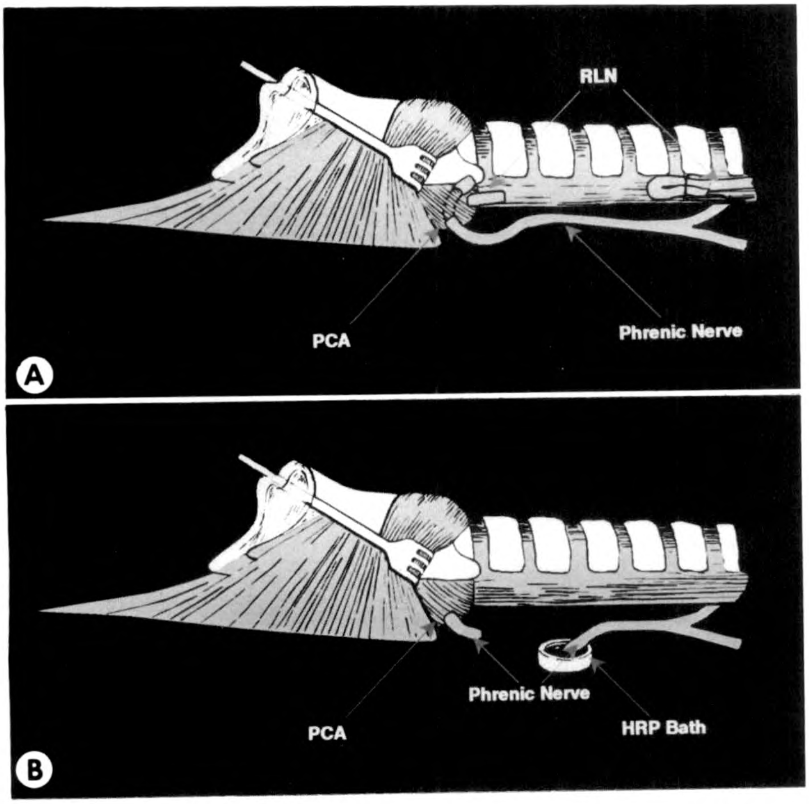

Fig 1. Diagrammatic representation of laryngeal reinnervation procedure. A) Sectioned recurrent laryngeal nerve (RLN) and phrenic nerve implanted in posterior cricoarytenoid muscle (PCA). B) Cut end of phrenic nerve exposed to horseradish peroxidase (HRP) bath.

4. Reexploration, examination by electromyography (EMG) of the PCA muscle, and retrograde labeling of the phrenic motoneurons.
5. Histologic verification of reinnervation by phrenic motoneurons.

The cats were lightly sedated with intramuscular ketamine hydrochloride (10 mg/kg) and diazepam (0.1 mg/kg). Direct laryngoscopy was performed to confirm normal vocal cord movement. Endotracheal halothane and nitrous oxide anesthesia was used. The phrenic nerve was identified and followed into the mediastinum and transected as far inferiorly as possible (Fig 1A). The phrenic nerve in the cat originates from 2 cervical roots (C-5 and C-6). In order to obtain adequate mobilization it was necessary to transect the inferior root. Thus, the reinnervating axons were derived from cervical root C-5. The left recurrent laryngeal nerve was located in the tracheoesophageal groove and followed to its insertion in the PCA muscle. The nerve was transected close to its insertion and approximately 1 cm of the nerve was excised. The proximal end was folded back on itself, sutured, clamped, and cauterized. The PCA muscle was visualized posterior to the thyroid lamina. The inferior constrictor muscle was either retracted superiorly or, in some cases, partially transected. An 8-0 silk suture was passed through the perineurium at the distal end of the phrenic nerve. The suture was then passed through the PCA muscle in a medial to lateral direction and the phrenic nerve was drawn through the muscle belly. The end of the nerve was then transected and allowed to retract into the muscle belly. When the nerve was in good position it was secured with fibrin glue in the tracheoesophageal groove and at its insertion into the PCA muscle. The remaining fibrin glue was used to secure the skin flaps. A multilayered closure using interrupted sutures was then performed. Within 2 weeks following the original operation, the cats were again lightly sedated and a direct laryngoscopy was performed to confirm left vocal cord paralysis.

Three to 4 months following the original procedure, the cats were again lightly sedated and a direct laryngoscopy was performed. The left vocal cord was visualized to determine if abduction had been restored and if it was coordinated with respiration. If the left vocal cord was still paralyzed, the reinnervation period was prolonged by at least 1 month, and maximally to a total survival time of 8 months.

Reexploration was carried out between 6 and 8.5 months after attempted reinnervation. The implanted phrenic nerve was located immediately inferior to the larynx in the tracheoesophageal groove. This nerve was then traced cephalad to its insertion into the PCA muscle. A Teflon-coated tungsten rod (tip diameter 0.28 mm) was placed into the PCA muscle on the reinnervated side, close to the insertion of the implanted phrenic nerve, and a muscle recording was

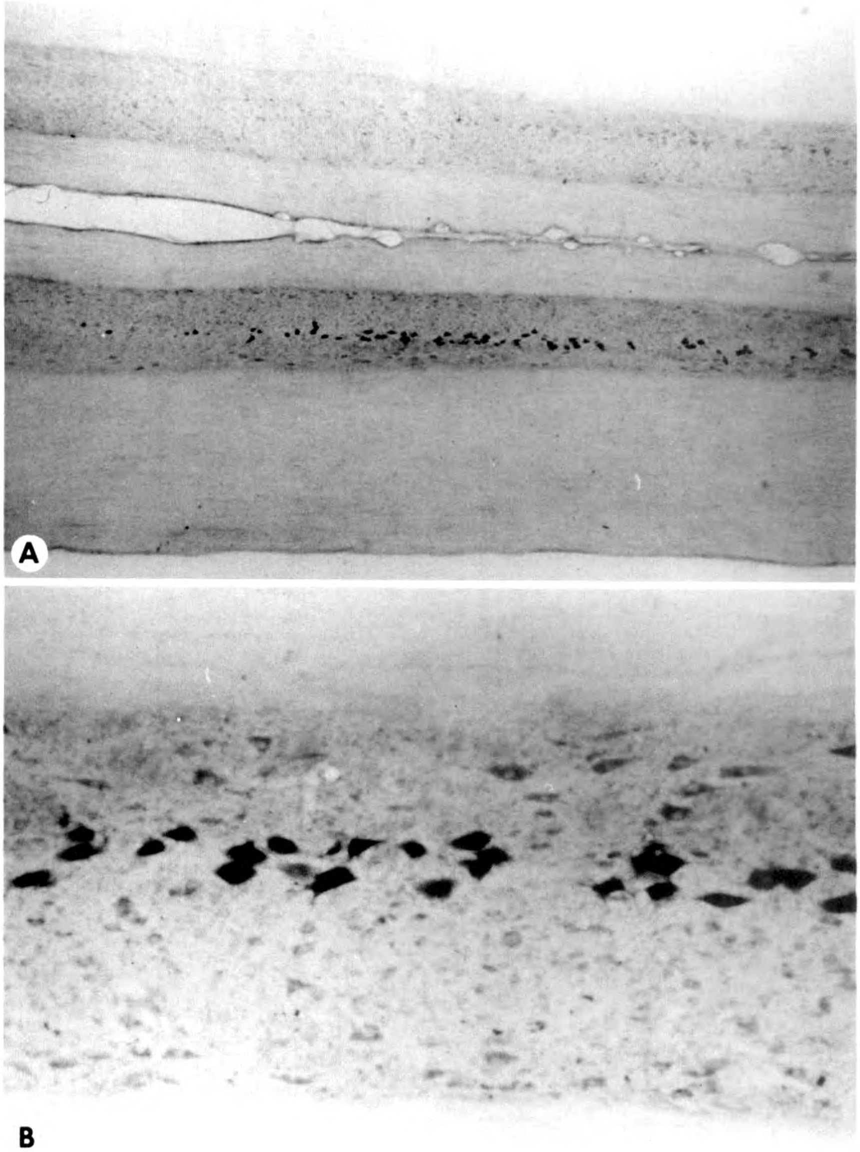

Fig 2. Photomicrographs at C-5. A) Left cervical cord showing labeled phrenic motoneurons on left side. B) High-power, showing labeled neurons.

made with a DISA Neuromatic 2000. The PCA electromyogram was recorded during calm respiration and during forced respiration induced by temporary obstruction of the endotracheal tube. The implanted phrenic nerve was then transected during the inspiratory phase of EMG activity.

The immediate loss of activity was accepted as evidence for phrenic reinnervation. A small dish was formed of dental wax and secured to the connective tissue close to the distal stump of the left phrenic nerve (Fig 1B). The cut end of the nerve was placed into the dish, which was filled with 50 μL of a 50% horseradish peroxidase (HRP, Sigma type VI) solution in normal saline. Following the protocol of Gordon and Richmond,[11] the nerve stump was exposed to this bath for 4 hours and then flushed with saline to prevent diffusion of the tracer to neighboring structures. The dish was then removed, the wound closed in layers, and the animal permitted to recover and survive for another 5 to 8 days. After that time the animals were deeply anesthetized with phenobarbital sodium (50 mg/kg) and perfused transcardially with 0.5% sodium nitrite in warm saline followed by a fixative consisting of 2% paraformaldehyde and 1.2% glutaraldehyde, and then by the same fixative with the addition of 10% sucrose. The cervical spinal cord was removed and submersed in the same fixative with 30% sucrose overnight. Serial horizontal 50-μm frozen sections of segments C-4, C-5, and C-6 were cut and reacted with tetramethyl benzidine–glucose oxide[14] and counterstained with 0.04% thionine. In 2 instances the cats died prior to completion of the above procedure. In both cats the distal portion of the reinnervating left phrenic nerve was removed and fixed for at least 1 week in fixative by immersion.

SUMMARY OF RESULTS FOR 12 CAT LARYNGES REINNERVATED WITH PHRENIC NERVE

Cat No.	*Reinnervation Time (mo)*	*Direct Laryngoscopy*	*Reexploration Findings*	*EMG*	*Label*
1	6	Abduction	Implanted	2	+++
2	6	Abduction	Implanted	2	++
6	7.5	Abduction	Implanted	1	++
8	8	Abduction	Implanted	1	++
9	8	Abduction	Implanted	1	++
11	7	Abduction	Implanted	1	+++
10	8	Abduction	Implanted	1	Death; axons*
7	7.5	Abduction	Implanted	1	Death; axons*
4	6	Abduction	Implanted	1	0
5	6.5		Pulled out		0
3	6.5		Neuroma, 2 rootlets	2	0
12	8.5		Neuroma, small branch	1	+

EMG — electromyography, 1 — real-time EMG showed loss of signal following nerve transection during inspiration, 2 — repeat EMG showed loss of signal following transection, 0 — none, + — weak, ++ — moderate, +++ — strong.

*Cross section of nerve showed myelinated axons where nerve entered posterior cricoarytenoid muscle.

These specimens were then processed histologically and stained with the Solochrome cyanine technique and safranine. Transverse 20-µm paraffin sections were examined for the presence of myelinated axons. Diameters of the entire myelinated axons were measured under a 40× objective to compensate for an assumed 30% tissue shrinkage due to dehydration and fixation.

RESULTS

Reinnervation was considered to be totally successful if 1) normal vocal cord abduction occurred on inspiration, as demonstrated on direct laryngoscopy, 2) PCA muscle EMG demonstrated reinnervation, and 3) horseradish peroxidase labeling of the phrenic nerve nucleus was demonstrated.

Standard signs of reinnervation were observed, including giant spikes during quiet respiration. When an increased motor drive was induced by obstructing the endotracheal tube temporarily for 30 to 90 seconds, there was a disorderly recruitment pattern, with larger spikes often being recruited earlier than smaller spikes. (Both observations are characteristic for reinnervated muscle.) Fibrillations were never seen. In 8 cats the phrenic nerve was cut at its entry into the PCA muscle shortly after initiation of a long (more than 1 second) inspiratory phase of activity on EMG. The motor unit activity on EMG disappeared immediately after nerve transection in every case.

Figure 2A illustrates the phrenic motoneuron column in the left cervical spinal segment C-5 of a cat with label exposure to the cut distal end of the left implanted phrenic nerve. After a survival time of 5 days the majority of motoneurons, shown in this horizontal section, were retrogradely labeled and projected, therefore, into the PCA muscle. The labeled motoneurons are shown at greater magnification in Fig 2B. The label outlined the perikarya and, in many cases, large portions of the dendritic tree. Such labeling was exclusively observed in the phrenic motoneuron column.

The reinnervation procedure was classified as a failure if, on direct laryngoscopy, there was no evidence of vocal cord abduction.

The results of the 12 procedures are summarized in the Table. Cats 1, 2, 6, 8, 9, and 11 (6 out of 12) were considered to be totally successful. In these cats there was abduction on direct laryngoscopy and positive findings on EMG and labeling. Cats 7 and 10 were almost certainly successfully reinnervated, as shown by the presence of abduction and positive findings on EMG. However, both died prior to completion of the labeling procedure. In these 2 cats the implanted nerve was stained and demonstrated myelinated axons, and therefore, we have chosen to consider the implantations successful. The myelin diameters were fairly homogeneous, ranging from 8.0 to 14.5 µm, with the myelin-axon ratio being in the normal range for motor nerves. Thus, the left PCA muscles were supplied by functioning motor nerves in these 2 cats. In cat 4, the evidence for reinnervation is limited to direct laryngoscopy and EMG. The disappearance of EMG spike activity after nerve sectioning provided decisive evidence in this cat that the PCA motor unit activity depended on the implanted phrenic nerve. Thus, this case was also successful in spite of our failure to label the motoneurons retrogradely. This conclusion is further supported by the operative exploration protocol. A careful operative exploration was extended back to the cervical root supplying the left phrenic nerve in all cats.

Cats 3, 5, and 12 did not show evidence of reinnervation on direct laryngoscopy. On reexploration of cat 5 it was obvious that the nerve had completely pulled out of the PCA muscle, and there was no evidence of reinnervation on EMG. Cat 12, on reexploration, also showed that the nerve had pulled out of the PCA muscle. There was, however, a neuroma at the terminal end of the phrenic nerve, and arising from this there was a small branch that grew from the neuroma to the muscle body. Electromyography demonstrated reinnervated PCA muscle, and when the branch was sectioned during real-time EMG, the signal was lost. Histochemical staining verified that these neurons did arise from the phrenic nerve nucleus. Cat 3 also failed to show abduction on direct laryngoscopy. On reexploration a neuroma was found, as in cat 12, and there were 2 rootlets passing into the PCA muscle. Electromyography showed reinnervation of the PCA muscle. When these rootlets were sectioned the EMG signal was lost. Histochemical staining, however, failed to show evidence of phrenic nerve reinnervation.

DISCUSSION

Our observations indicate that vocal cord abduction during inspiration can be achieved in the acutely paralyzed larynx. In all cases in which reinnervation was interpreted as successful, there was no indication that the implanted phrenic nerve might have become mechanically dislodged from the PCA muscle belly during the survival period. In 6 cats all criteria for reinnervation were met. In an additional 3, vocal cord abduction was visible and the EMG activity in the reinnervated PCA muscle was proven to be derived from the implanted nerve. The only evidence missing was retrograde labeling of phrenic motoneurons in the spinal cord. While positive labeling certainly proves reinnervation, its absence does not disprove it. Our labeling failure in cat 4 is unexplained, as are many unsuccessful labeling experiments in laboratories engaging in these methods. In 2 cats no labeling could be attempted because the animals died during the second operation. These deaths were not related to the reinnervation procedure. In both cases, there was a respiratory failure after transection of the reinnervating nerve and extubation. Since such conditions would not prevail if this method were employed for therapeutic purposes, there is no reason to interpret these incidents as alarming indicators for possible side effects.

In 2 of the 3 cats without visible abduction of the vocal cords, there was EMG evidence for reinnervation, and in 1 there was additional morphological evidence. Since these PCA muscles were only innervated by small nerve rootlets, the innervating neuron population was probably too small for visible cord movements. That does not prove that these cords were entirely immobile, since a maximal motoneuron activity cannot be expected under anesthesia or sedation, without the need for deep inspiration.

The 3 cases without visible vocal cord abduction illustrate that the key for success with this procedure is meticulous operative technique. Reinnervation appears to depend on the maintenance of a viable phrenic nerve end within the muscle belly. To this end, sufficient nerve mobilization seems critical. In an unpublished preliminary series leading to the presented experiments, we determined that the probability for dislodging the nerve from the muscle was inversely related to the available nerve length. A further informal impression was that fixation of the nerve by sutures may have inhibited the axons' sprouting into the muscle, possibly because of some mechanical obstruction. This is easy to imagine for the phrenic nerve of cats, in which the diameter is small relative to even the finest suture material. The success rate in dogs, in which the sutured phrenic nerve was thicker, was also poor, however. In the present series sutures at the reinnervation site were entirely avoided and the nerves were fixed in position with fibrin glue. As a result, reinnervation was successful in all cases in which nerve fixation was, in fact, achieved. A further improvement may be expected if the fixation of nerve to muscle becomes more reliable. Likely factors are the experience of surgeons with the fibrin glue and the surface area of contact between muscle, nerve, glue, and surrounding tissue.

CONCLUSIONS

The purpose of this study was to develop and assess a technique for restoring physiologic vocal cord abduction for bilateral laryngeal paralysis. In the current series of experiments we have shown that in the freshly denervated larynx of the cat, the phrenic nerve can be used to reestablish coordinated vocal cord abduction. The source of this reinnervation was confirmed histologically by retrograde labeling techniques. The use of fibrin glue to hold the phrenic nerve in position avoided severe trauma to the distal end of the phrenic nerve. Implanting the nerve directly in the PCA muscle rather than anastomosing it to the recurrent laryngeal nerve avoids the problem of synkinesis and poor functional reinnervation. The results of this study can be applied only to the situation of recent denervation of the larynx. However, some research has suggested that atrophy of the denervated PCA muscle may not occur for at least 1 year.[15] If this is the case, then reinnervation would be possible for up to 1 year, thus increasing the feasibility of clinical application. We believe this technique should be considered as an alternative to vocal cord lateralization or tracheotomy.

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HYDROXYLAPATITE LARYNGEAL IMPLANTS FOR MEDIALIZATION

PRELIMINARY REPORT

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Laryngeal implantation for medialization has improved our ability to manage the patient with vocal fold motion impairment. We present preliminary data evaluating the use of preformed hydroxylapatite laryngeal implants and instrumentation for rapid determination of implant size and position. A window in the thyroid ala is created by means of a standard fenestra template. One of 5 prosthesis templates is inserted through the window for determination of correct size and position. The corresponding implant is then inserted and secured with a hydroxylapatite shim. Thirty-five patients have been implanted for vocal fold paralysis, and 4 patients were implanted for soft tissue deficits or bowing. Thirty-one of 35 patients have reported subjective improvement (89%). Improvement was demonstrated in 13 of 15 (87%) patients with complete preoperative and postoperative objective voice function measurements. Complications include 1 implant extrusion and 1 case of airway obstruction secondary to edema. Preliminary results indicate that prefabricated hydroxylapatite implants are effective for medialization thyroplasty. Advantages include a readily available implant selection, rapid determination of correct size and position, and improved implant stabilization with a hydroxylapatite shim.

KEY WORDS — **hydroxylapatite, laryngeal implantation, medialization thyroplasty, vocal fold paralysis.**

INTRODUCTION

The disability of vocal fold paralysis ranges from imperceptible to profound. Classically, aspiration of saliva and ingested materials, decreased exercise tolerance, and, most important, an inability to project the voice form the clinical triad. The cause of recurrent laryngeal nerve (RLN) dysfunction, occasionally combined with a superior laryngeal nerve (SLN) deficit, may be secondary to primary neuronal disruption, secondary to more global neurologic disorders, or an end product of the aging process.

Many therapeutic maneuvers have been conceived to restore bulk to or reposition the paralyzed fold. Endoscopic deposition by needle of viscous materials such as glycerin, Teflon paste, Gelfoam paste, fat suspension, and collagen have been used with measured success. Certainly, Teflon paste has been held as the accepted standard for 25 years. As laryngeal framework surgery evolves, however, prostheses carved from Silastic and other alloplastic materials are being used more frequently.

Problems associated with vocal fold augmentation, especially with type I thyroplasty (laryngeal framework surgery), include 1) imprecision of augmentation in terms of anatomic orientation or inadequate medialization of the paralyzed fold, 2) migration of the prosthetic material, 3) soft tissue reactivity to implant material, 4) the potential for extended surgical time caused by on-site fabrication of a prosthesis that may result in an unpredictable end result, and 5) poor stabilization or fixation of the prosthesis after the optimal position is established.

To address these potential problems, instrumentation for rapid sizing and positioning, hydroxylapatite implants to minimize tissue reactivity, and locking shims for stabilization have been developed. This paper will outline our early experience with these preformed hydroxylapatite prostheses. We will describe the uniform preoperative workup, which includes neurologic evaluation, closed flow volume loop, selective electromyography (EMG) if incomplete neuronal disruption is a question, videofluoroscopy, stroboscopy, and vocal function testing. The surgical sequence is described, and follow-up results are reported.

METHODS

Patient Selection. Thirty-nine patients have undergone implantation with hydroxylapatite prostheses for management of incomplete glottic closure. The mean age of this group was 54. There were 24 men and 15 women. The causes of the patient's dysphonia are categorized in Table 1. Thirty-five patients presented with vocal fold paralysis, and 4 patients presented with soft tissue deficits (3) or bowing (1). Of the 35 patients with vocal fold paralysis, 19 had isolated RLN injuries, and 16 patients had combined

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TABLE 1. CAUSES OF INJURY

Causes	*No. of Pts*
Thyroid surgery	7
Thoracic procedure	10
Tumor resection	10
Trauma	4
Idiopathic	3
Cerebrovascular accident	1
Other Soft tissue deficit Vocal fold bowing Sulcus	4
Total	39

TABLE 2. PRESENTING SYMPTOMS

	Aspiration	*Dysphagia*
Mild	7	9
Moderate	6	7
Severe*	4	4

*All combined recurrent laryngeal nerve–superior laryngeal nerve injuries.

SLN-RLN injuries. Thirty patients presented with long-standing injuries (>12 months), and 5 patients presented less than 6 months after injury. Two patients presented with complaints of persistent hoarseness after inadequate or misplaced Teflon injection.

All patients complained of dysphonia consisting of breathiness and loss of vocal projection or pitch control. Twenty patients complained of dysphagia, and in 17 patients this was accompanied by aspiration (Table 2). Aspiration and dysphagia are categorized as mild, moderate, or severe. Mild dysphagia is simply a subjective complaint of difficulty swallowing or occasional choking not requiring dietary modification or therapeutic intervention. Moderate aspiration and dysphagia include symptoms necessitating dietary modification or swallowing therapy. Severe aspiration or dysphagia requires feeding tube placement for alimentation to maintain weight or prevent pulmonary complications of aspiration. The majority of patients presented with mild to moderate symptoms. There were 4 patients with severe dysphagia and aspiration, all of whom presented with combined RLN-SLN injuries as well as associated ipsilateral cranial nerve IX, XI, and XII deficits.

Forty-two procedures were performed altogether. Thirty-five patients underwent unilateral medialization procedures. Bilateral procedures were performed in 4 patients with soft tissue deficits (3) or bowing (1), and 3 patients were revised.

Diagnostic Procedures and Instrumentation. Subjects were examined 1 or 2 weeks preoperatively and 1 month and 6 months postoperatively. Voice evaluations consisted of objective measurements of mean fundamental frequency, pitch range, maximum phonation duration, and perceptual judgments of voice quality.

Measurements of fundamental frequency and pitch range were obtained with the Visi-Pitch model 6095/6097 (Kay Elemetrics Corp, Pine Brook, NJ) interfaced with an Everex 386sx computer. Mouth-to-microphone distance is maintained at approximately 2.5 to 5.0 cm. The fundamental frequency, or habitual pitch, is calculated as the mean frequency during three 20-second speech tasks: counting, reading, and monologue. Fundamental frequency is measured as the mean frequency across the 3 trials. Pitch range is obtained by instructing the subjects to individually hum up and then down the musical scale to their extreme limits. The pitch range is then defined by the lowest and highest extents achieved in 3 attempts, converted into semitones. Maximum phonatory duration from 3 trials is obtained for sustained voiced phonemes following deep inspiration. The maximum phonation duration is calculated for sustained /a/.

A 2-tailed, paired Student's *t* test was used for statistical analysis (True Epistat, Version 4.0, Richardson, Tex). Preoperative and postoperative comparisons were made for mean fundamental frequency, pitch range, and maximum phonation duration in 15 patients with vocal fold paralysis. Comparisons were also made between patients with isolated RLN injury and combined RLN-SLN injury.

Stroboscopy is performed with a Nagashima 70° rigid fiberoptic scope or a Pentax FN-13S flexible fiberoptic scope mated to a laryngostroboscope (Nagashima LS-3A). The stroboscope is triggered by the subject's fundamental voice frequency in the standard fashion. Recordings are obtained during vowel production (/i/ and /a/) in the chest register, head register, and falsetto. Trials are performed at both minimum and maximum loudness levels. Stroboscopic results are recorded on ¾-in videotape and analyzed by the investigators at a later date. The investigators are not blinded to the subject's identities. The presence or absence of the mucosal wave, wave amplitude, phase, and glottic closure are evaluated.

Laryngeal EMG is performed in all patients with idiopathic paralysis and patients presenting less than 12 months after injury. A percutaneous approach through the cricothyroid membrane using 37-mm, 26-gauge, Teflon-coated monopolar electrodes is employed. A reference electrode is placed over the clavicle and a ground over the chest. All patients are studied in the awake state. Recordings are obtained from the cricothyroid muscle and thyroarytenoid or

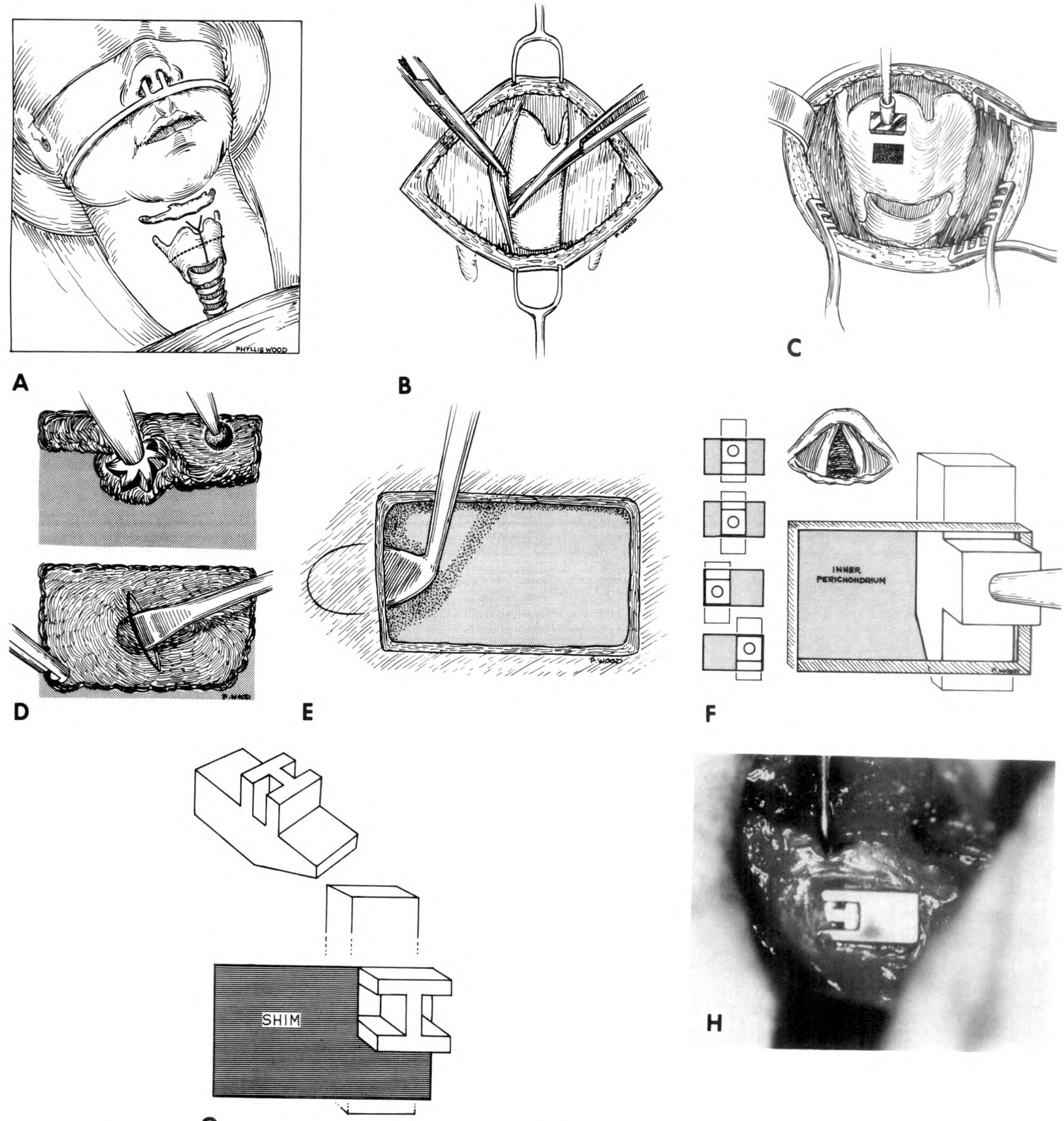


Fig 1. Technique for medialization thyroplasty. A) Incision. B) Exposure of thyroid lamina. C) Cautery applied to window template outlining fenestra. D) Removal of cartilage and osteoid material from fenestra. E) Elevation of inner perichondrium with blunt dissector. F) Appropriate size and position of implant are determined with sizing template. G,H) Prosthesis in place and secured by shim.

lateral cricoarytenoid muscle. Samples are taken at rest and during sustained vowel production (/i/) at low intensity (in the chest register) and high intensity (in the head register or falsetto) for maximal recruitment. The needle is repositioned for 3 separate site recordings in each muscle.

Denervation is determined to be present when absence of voluntary motor unit action potentials, fibrillation potentials, positive sharp waves, or isolated complex repetitive discharges are recorded on EMG. Reinnervation is diagnosed when polyphasic waves and/or partial interference patterns are observed with or without denervation potentials. A normal interference pattern obtained during maximal recruitment, combined with a lack of the abnormal

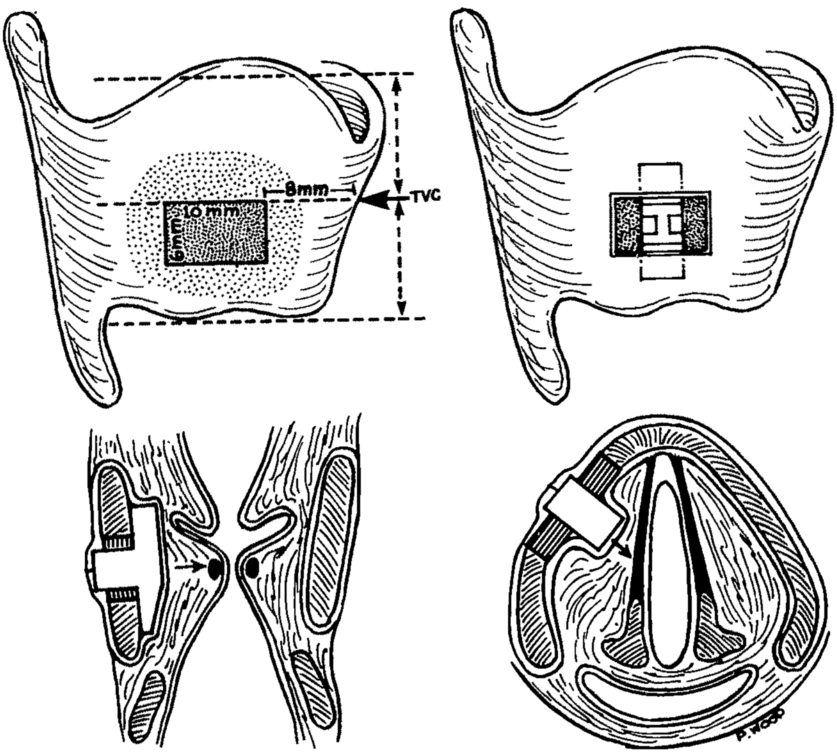


Fig 2. Medialization thyroplasty. Horizontal fenestra with implant in vertical position and beveled surface of implant directed inferiorly to accommodate conus elasticus.

patterns noted above, is judged consistent with normal innervation.

Videofluoroscopic evaluation of swallowing is performed in all patients with history or symptoms suggesting aspiration. Flow volume loops are obtained in all patients prior to surgical intervention. Postoperatively, flow volume loops are obtained only if the patients have symptoms suggesting worsening of their airway symptoms. Videofluoroscopy is performed postoperatively in all patients with a preoperative study demonstrating laryngeal penetration or aspiration.

Methods of Surgical Procedure. With the patient in the supine position and prepared for a sterile procedure, a paramedian horizontal incision is outlined over the middle aspect of the thyroid lamina (Fig 1). Local anesthesia is administered subcutaneously and in 4 quadrants over the ipsilateral lamina. A 5- to 6-cm incision is made through the platsyma. Superior and inferior flaps are elevated in the subplatysmal plane, exposing the thyroid notch and inferior border of the thyroid cartilage. The strap muscles are split in the midline and retracted laterally off the thyroid lamina, leaving the outer perichondrium intact. A single large skin hook is implanted in the anterior-superior aspect of the contralateral ala and retracted laterally, providing exposure of the ipsilateral lamina. The perichondrium is scored with electrocautery applied to a window template placed 10 mm (in men) or 5 mm (in women) posterior to the ventral midline, with the superior edge at the level of the vocal fold. The outer perichondrium is incised and elevated off the window. Cartilage and osteoid material are removed precisely from the rectangle. Where ossification has occurred, that portion within the window may be drilled out, or removed with a Kerrison punch. Regardless, care must be taken to preserve the inner perichondrium, which is now elevated in circumferential fashion off the thyroid lamina by means of a No. 4 Penfield elevator. One of the 5 sizing prosthesis templates (3 to 7 mm) is inserted through the window and rotated 90° with the bevel directed inferiorly (Fig 2). All retractors are removed and the patient asked to phonate while the template is placed in all 4 quadrants of the window to determine optimal position. Smaller or larger templates may be selected as needed. The implant may be placed in a horizontal position with the bevel directed anteriorly. Once the appropriate size and position have been determined, the retractors are replaced, the implant is inserted, and if the voice is optimal, the implant is secured with the corresponding shim. If the window adheres to the prescribed dimension, the shim will fit securely, preventing migration of the implant. The wound is then irrigated with antibiotic solution. A $^1/_4$-in Penrose drain is placed deep to the strap muscles and brought out through the incision. Strap muscles, platysma, and skin are closed in the routine manner. An absorbant, sterile dressing is applied and left in place for 24 hours, and then the Penrose drain is removed. Decadron (8 mg) is given preoperatively to

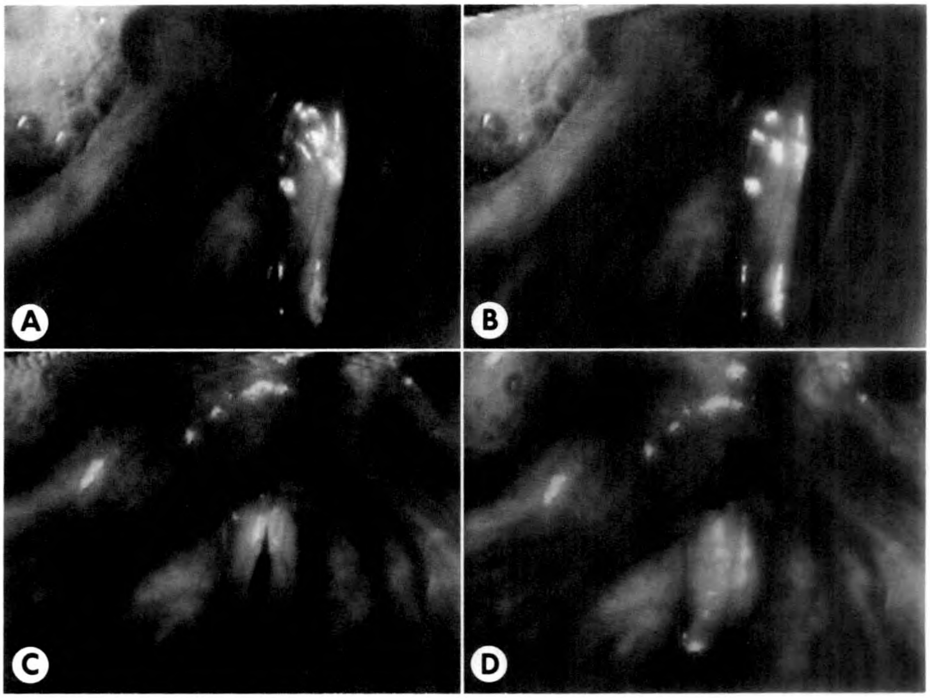


Fig 3. Stroboscopic evaluation of patient with combined recurrent laryngeal nerve (RLN)–superior laryngeal nerve (SLN) injury resulting in left vocal fold motion impairment. A,B) Stroboscopic view during sustained vowel phonation. There is large gap involving entire length of true vocal folds. There is aperiodic motion of both vocal folds. C,D) Posterior stroboscopic examination of same patient following left medialization thyroplasty. Bilateral mucosal waves are now present with complete glottic closure during closing phase.

minimize edema. Prophylactic antibiotics are continued for 5 days.

RESULTS

For reporting purposes, only the 35 patients treated for laryngeal paralysis were evaluated. Subjective improvement following the initial procedure was noted in 31 of 35 patients (89%) with vocal fold paralysis. Stroboscopic evaluation demonstrated complete glottic closure with a mucosal wave present in 28 of 35 patients (80%) with vocal fold paralysis (Fig 3). Partial closure was obtained in the remaining 7 patients. Revision was performed in 3 patients. Two of these patients were satisfied with the outcome following revision (Table 3). Complete closure was obtained in 2 of the 3 patients undergoing revision and in the 2 patients with previous Teflon injection. The overall subjective improvement rate, therefore, increased to 94% (33 of 35). The 4 patients with dysphonia secondary to bowing or soft tissue deficits improved subjectively and by stroboscopic examination (Fig 4).

Preoperative and postoperative (1 to 3 months) objective assessment was obtained in 15 patients with vocal fold paralysis. Eight patients had isolated RLN injury, and 7 presented with combined RLN-SLN injuries. Group analysis demonstrated a significant increase in maximum phonation duration (Fig 5A). This is true for both the isolated RLN injury group and the combined RLN-SLN injury group. Significant improvement in pitch range was also observed for both isolated RLN injury and combined RLN-SLN injury patients (Fig 5B). The mean fundamental frequency did not change for either group of patients (Fig 5C). When gender-specific comparisons were made, there was no significant change in mean fundamental frequency.

Subjective improvement in dysphagia occurred in 17 of 20 patients (85%). Subjective improvement in aspiration occurred in 15 of 17 patients (88%). In all 4 patients with severe dysphagia and aspiration, improvement was documented by videofluoroscopy. Although 1 patient remains gastrostomy tube–dependent, this individual did have marked improvement in management of secretions.

Complications were encountered in 2 patients. The

TABLE 3. SURGICAL FAILURES AND REVISION RESULTS

Pt No.	*Age*	*Sex*	*Injury*	*Implant Size (mm)*	*Management*	*Outcome*
1	64	M	Isolated RLN	4	Revised with 6-mm implant	No improvement
2	24	M	Combined RLN-SLN	6	Revised: position change and palatal flap	Improved
3	29	M	Combined RLN-SLN	5 R, 3 L	No revision	No improvement
4	44	F	Cembined RLN-SLN	4	Revised with 7-mm implant	Improved

RLN — recurrent laryngeal nerve, SLN — superior laryngeal nerve.

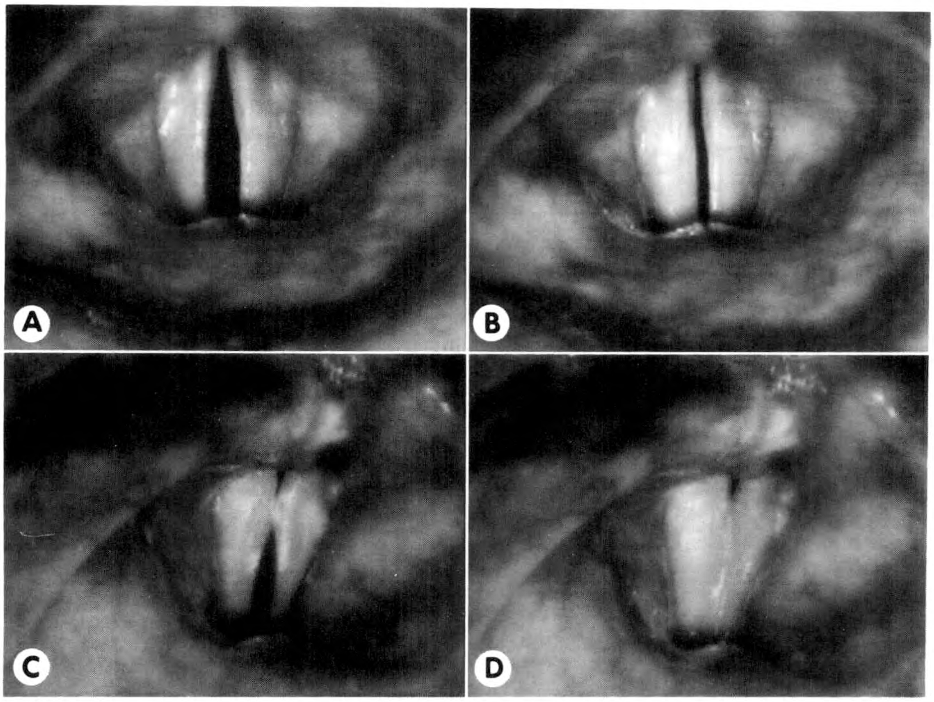


Fig 4. A,B) Stroboscopic evaluation during sustained vowel phonation in patient following excision of left vocal fold nodule. There is absence of vibration on left side and loss of soft tissue, resulting in persistent gap involving entire length of true vocal folds. C,D) In same patient, following left medialization thyroplasty, mucosal wave is now present on left side, and complete glottic closure is obtained during closing phase.

total complication rate in 42 procedures was 4.8%. Endolaryngeal extrusion occurred in 1 patient. One year following implantation, this patient sustained severe blunt trauma to the neck with immediate hoarseness. Two days later the patient developed a paroxysm of coughing and extruded the implant into the oral cavity. The patient's voice remained adequate 2 months following extrusion, and there were no other sequelae. A partially compromised airway secondary to edema was observed in 1 patient, necessitating admission 48 hours after the procedure. The patient was managed conservatively with humidification, oxygenation, steroids, and intravenous antibiotics. The edema resolved, and the patient was discharged 48 hours after admission.

DISCUSSION

Incomplete glottic closure may result from vocal fold motion impairment, soft tissue deficits, vocal fold bowing, or atrophy associated with neuromuscular disease. Management of incomplete glottic closure includes speech therapy, vocal fold injection, thyroplasty, and various reinnervation procedures. Medialization thyroplasty, as popularized by Isshiki et al,[1] is rapidly becoming the standard for treatment of glottic insufficiency. Advantages of medialization thyroplasty include 1) performance of the procedure under local anesthesia, 2) optimal surgical positioning, allowing for intraoperative assessment of vocal function, 3) placement of the prosthesis lateral to the inner perichondrium, preserving the structural integ-

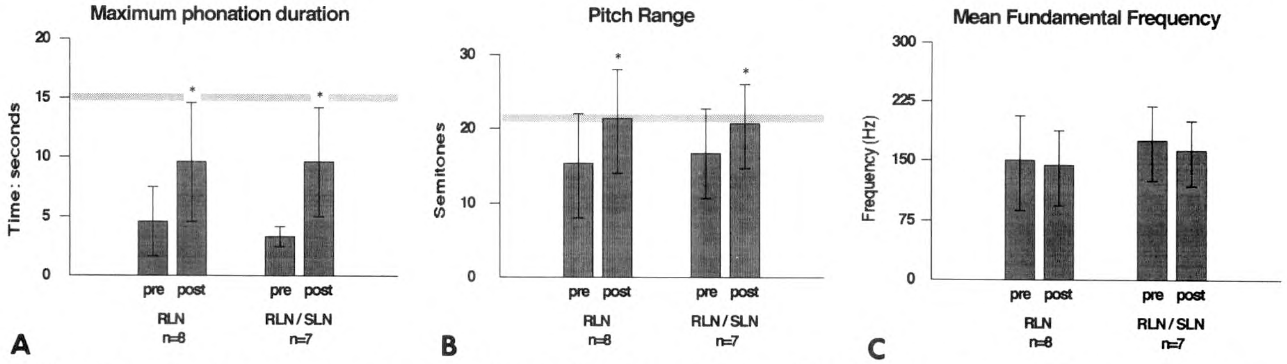
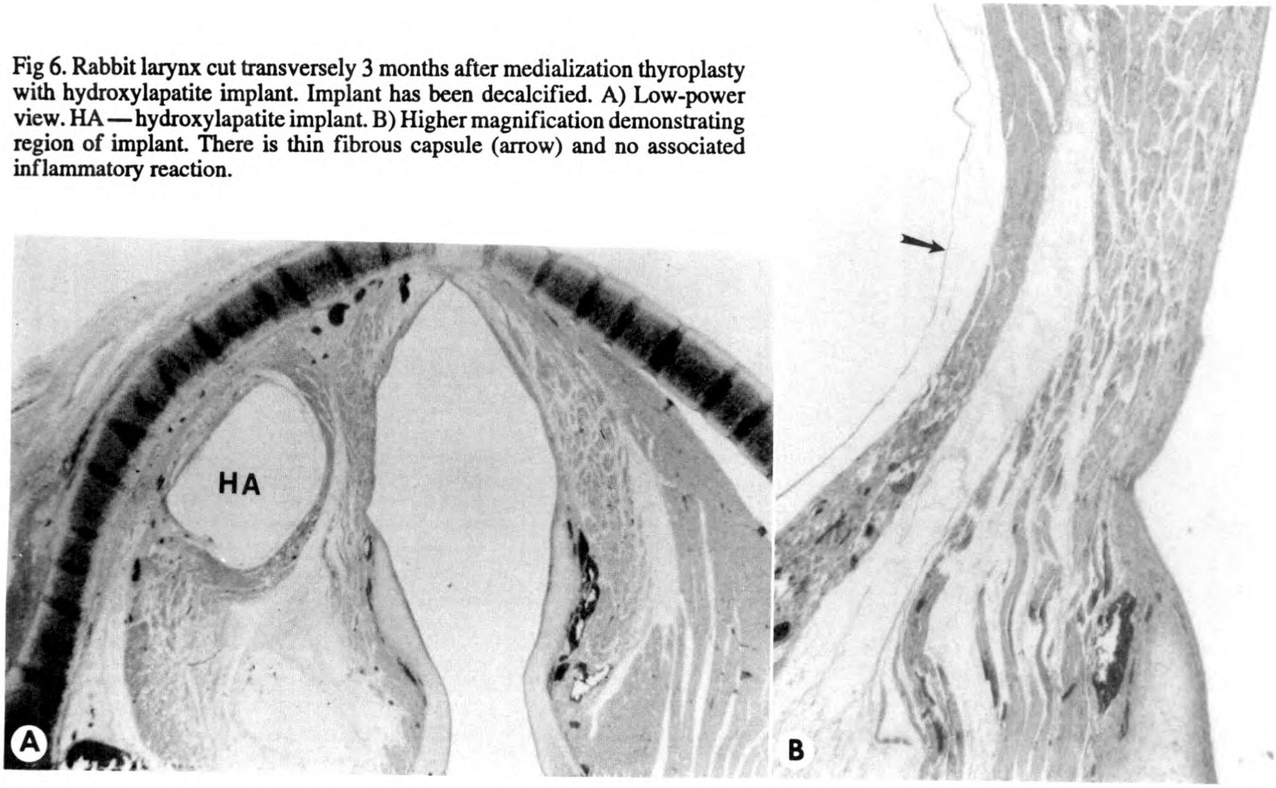


Fig 5. Test results in 15 patients with vocal fold paralysis before and after medialization thyroplasty. A) Maximum phonation duration. Significant improvement (asterisks) is observed in isolated RLN group (p = .0152) and in combined RLN-SLN group (p = .0145). Shaded line — normal values. B) Pitch range. There is significant improvement (asterisks) in patients with isolated RLN injury (p = .0345) and in combined RLN-SLN group (p = .0318). Shaded line — normal values. C) Mean fundamental frequency. There is no difference in patients with isolated RLN injury (p = .5677) or combined RLN-SLN injuries (p = .6589). When patients were grouped according to gender, there was no significant difference in mean fundamental frequency before or after surgery.

Fig 6. Rabbit larynx cut transversely 3 months after medialization thyroplasty with hydroxylapatite implant. Implant has been decalcified. A) Low-power view. HA — hydroxylapatite implant. B) Higher magnification demonstrating region of implant. There is thin fibrous capsule (arrow) and no associated inflammatory reaction.



rity of the vocal fold, and 4) the potential reversibility of the procedure. Disadvantages of medialization thyroplasty include the following: 1) the procedure requires an open, external approach, 2) perioperative edema may compromise intraoperative assessment, 3) stabilization of the implant is at times difficult and extrusion may occur either externally or internally, and 4) soft tissue response to the implant material may ultimately compromise results. Furthermore, the procedure is technically difficult, and intubation for surgery subsequent to medialization may result in displacement of the prosthesis or mucosal erosion secondary to endotracheal tube pressure.

Procedural factors affecting the outcome of medialization thyroplasty include the size and shape of the implant, the position of the implant, maintaining proper position of the implant, and limiting the duration of the surgical procedure. Minimizing operative time is critical for obtaining optimal results.[2] Prefabricated implants and rapid determination of size and position intraoperatively will facilitate the procedure. While carved Silastic implants are used in most centers, the authors use a technique employing prefabricated dense hydroxylapatite implants with matched sizing templates, allowing rapid determination of the correct implant position and size.

The biocompatibility of hydroxylapatite has been demonstrated in both animal and human studies. Porous hydroxylapatite typically shows early ingrowth of fibrous tissue, osseointegration, and absence of an inflammatory response, while dense hydroxylapatite implants show complete fibrous encapsulation, with absence of bone growth or an inflammatory response.[3-5] Laryngotracheal reconstruction has been reported in animals and humans.[6,7] The soft tissue response to laryngeal implantation with hydroxylapatite prostheses in rabbits is currently being investigated (P.W. Flint and R. Corio, unpublished observations). Preliminary results at 3 months demonstrate thin fibrous encapsulation of the implant, with absence of an inflammatory response (Fig 6). Osteogenesis in the region of the fenestra has been observed and may aid in stabilizing the implant, limiting the risk of dislodgement or migration. Animals injected with Teflon demonstrated an intense granulomatous reaction similar to that observed in humans (Fig 7). The biocompatibility of hydroxylapatite for laryngeal reconstruction and medialization thyroplasty appears superior to that of Teflon.

Patient factors that may affect the outcome include the presence of combined RLN-SLN injuries, associated velopharyngeal insufficiency, other cranial nerve involvement, and previous surgical procedures (ie, Teflon injection). While patients with combined RLN-SLN injuries generally present with a greater degree of impairment with respect to phonation and swallowing, we found no significant difference between the isolated RLN group and the combined RLN-SLN group with respect to preoperative and postoperative

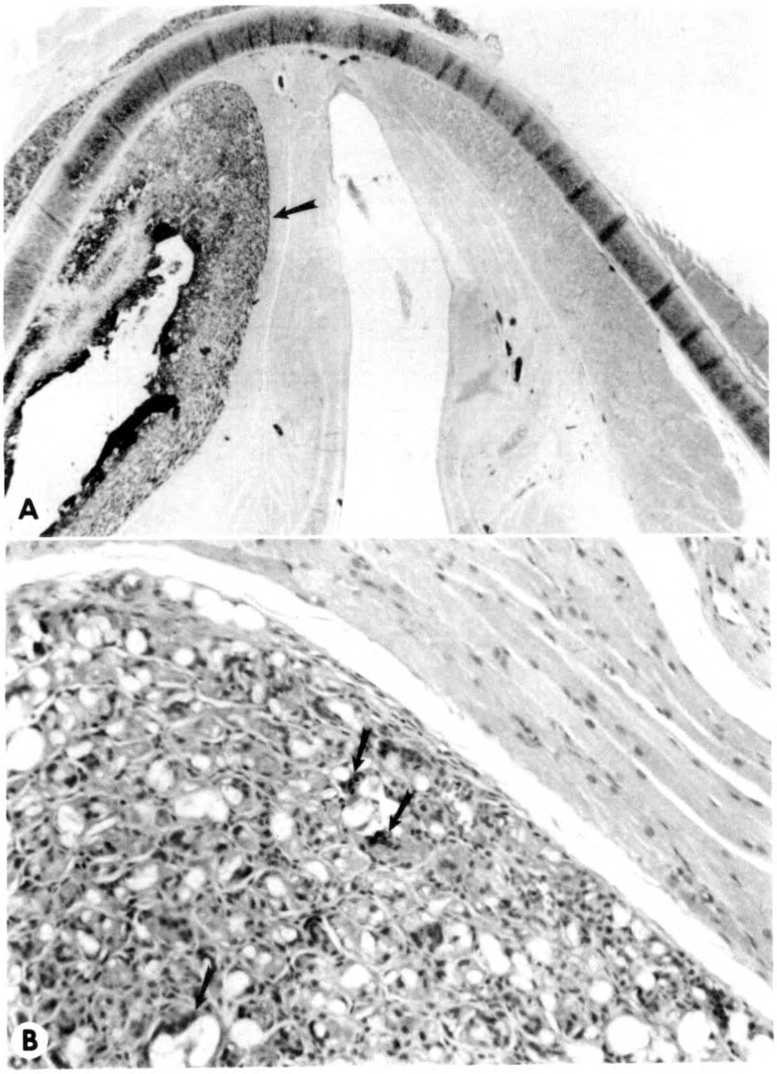


Fig 7. Rabbit larynx cut transversely 3 months after injection with Teflon for medialization. A) Low-power view. Arrow — Teflon. B) Higher magnification demonstrating granulomatous response to Teflon particles with foreign body giant cells (arrows).

vocal performance. Three of the 4 immediate failures, however, did have combined RLN-SLN injuries associated with other cranial nerve deficits. These patients are listed in Table 3. Two of the 3 patients improved following revision. One patient required repositioning of the prosthesis and correction of velopharyngeal insufficiency with a superiorly based pharyngeal flap. The second patient required a larger prosthesis for correction of incomplete closure.

The size of the implant used did vary with respect to the type of injury. Four-millimeter to 5-mm implants were used more often in isolated RLN injuries, whereas 5-to 7-mm implants were used in combined RLN-SLN injuries. Overmedialization is supported by Isshiki et al,[2] who found deterioration in voice quality over time as intraoperative edema resolved postoperatively. Where early medialization is performed, muscle atrophy may also result in voice deterioration in the postoperative period.

Prior injection with Teflon is not a contraindication to medialization with hydroxylapatite, although patients should be counseled that results may be compromised as a result of the increased mass associated with Teflon deposition. Two patients in this report had undergone previous injection with Teflon, and both patients experienced improvement in their symptoms after medialization thyroplasty.

Finally, because the prosthesis is placed lateral to the inner perichondrium of the thyroid lamina, the structural integrity of the vocal fold is preserved, allowing medialization in the presence of a mobile vocal fold. The 4 patients with soft tissue deficits or bowing were all improved subjectively, and improvement was demonstrated by videostroboscopy showing closure of the glottic gap.

CONCLUSION

The preformed, multiple-size hydroxylapatite vocal fold augmentation system presents an uncomplicated surgical solution to the problem of vocal fold augmentation. The goals of reduced operating time and stabilization of the prosthetic system are accomplished. The multiple-size measuring devices allow for rapid selection of the optimal-size prosthesis, adding an aspect of fine tuning to the surgical procedure. The bioactive response to hydroxylapatite, as contrasted to the known granulomatous response to Teflon and the potential for extrusion with Silastic, would appear to be an added advantage to this surgical methodology.

The absolute indication for vocal fold augmentation is symptomatic RLN paralysis. Previous augmentation with Teflon paste does not necessarily rule out consideration. Those individuals with more global neurologic deficits (parkinsonism) or dysphonia associated with aging (presbylaryngis), and patients with surgical soft tissue deficits, may benefit from this technology as well.

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CORRELATION BETWEEN STROBOSCOPY AND ELECTROMYOGRAPHY IN LARYNGEAL PARALYSIS

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Twenty patients with vocal fold motion impairment were reviewed to correlate the findings of electromyography (EMG) and stroboscopy. The causes of motion impairment were idiopathic, previous surgery with recurrent laryngeal nerve injury, neck and skull base trauma, and neoplasm. The EMG studies were analyzed to assess the status of innervation of the immobile vocal fold. The presence or absence of the mucosal wave prior to therapeutic intervention was determined with stroboscopic examination. Eight of 10 patients with EMG evidence of reinnervation or partial denervation were found to have mucosal waves, and 3 of 10 patients with EMG evidence of denervation were found to have mucosal waves. Six patients developed mucosal waves after surgical medialization, despite evidence of denervation by EMG criteria. These findings support the premise that tension and subglottic pressure, rather than status of innervation, determine the presence of the mucosal wave.

KEY WORDS — electromyography, laryngeal paralysis, stroboscopy.

INTRODUCTION

The otolaryngologist evaluating the patient with the immobile vocal fold addresses 3 issues. First, is the cause neurologic or mechanical? A more extensive workup searching for disease at other sites may be indicated if a neurologic lesion is suspected. Second, what is the patient's current functional status? The patency of the airway, the adequacy of glottic closure as it pertains to protection from aspiration and voice production, and the quality of voice itself are all important. Finally, what is the prognosis for recovery? This will determine not only the need for therapeutic intervention, but its timing as well.

The immobile vocal fold can be assessed by different modalities, each with its own applications and limitations. Indirect or fiberoptic laryngoscopy enables direct visualization of the airway. However, the phonatory vocal fold vibrations occur too rapidly to be assessed by the unaided eye,[1,2] and the status of vocal fold innervation can only be inferred from vocal fold motion and position.[3] As such, little prognostic information is available from this examination.

Laryngeal stroboscopy utilizes an electronically controlled, intermittent, high-intensity light to image the high-speed vibratory movements of the vocal fold during phonation.[1,2] The fundamental movement of the vocal fold during phonation is the mucosal wave, a rhythmic displacement of the mucosa over the fibromuscular body of the vocal fold in both the transverse and vertical planes.[4] This "glottic wave" was originally described in Bell Laboratory's high-speed motion pictures of phonating vocal folds made in 1938.[5] Three forces interact to form the glottic wave. When the glottis is closed during phonation, the subglottic pressure forces the glottis open and displaces the mucosal edges laterally. The elasticity of the vocal fold and the Bernoulli effect of the transglottic airflow subsequently draw the mucosa medially.[4] The "cover-body" model of the vocal fold describes a layering of soft, elastic mucosa and submucosa over the stiff, muscular body of the vocal fold.[6] This arrangement allows the glottic mucosa to move somewhat independently and enables the mucosal wave to occur. The mucosal wave is reliably present in the normally functioning larynx.

The "cover-body" theory of the mucosal wave predicts that the mucosa and the underlying fibrous fold must be of differing consistency for the wave to exist. It is also theorized that denervation of the vocal fold musculature leads to loss of the mucosal wave.[4] This is supported by observations in humans[7,8] and in studies of the denervated dog larynx.[9] It is presumed that reinnervation of laryngeal muscles results in the return of a mucosal wave.[4,7,8]

Laryngeal electromyography (EMG) can be used to objectively differentiate mechanical from neuro-

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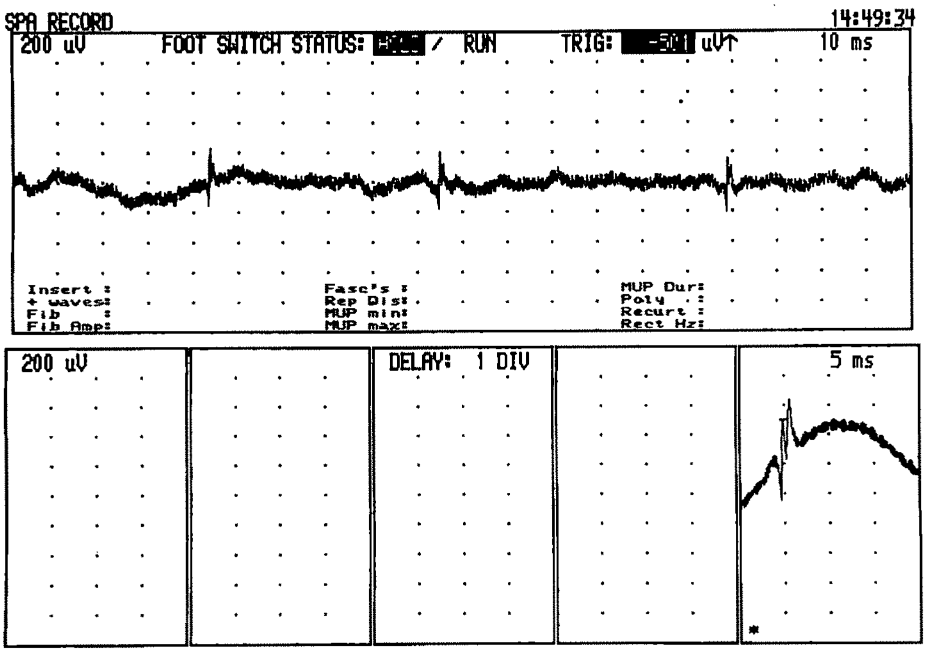

Fig 1. Fibrillation potentials recorded at rest from left thyroarytenoid muscle in patient with 18-month-old recurrent laryngeal nerve injury. Potentials are generated from fluctuations in resting membrane potential of denervated skeletal muscle fibers. They usually have amplitude of 20 to 300 µV and duration of less than 5 milliseconds (ms), and usually occur rhythmically at rate of 2 to 20 Hz. Potentials are biphasic or triphasic; initial phase is positive (downward deflection). Positive sharp waves (not shown) also occur in denervated muscle and primary disorders of muscle. They may occur as result of needle insertion, or spontaneously with regular intervals. There is initial rapid positive deflection (<1 ms) followed by slow change of potential in negative direction and small negative phase (upward deflection). Amplitude is slightly greater than that of fibrillation potentials, but may reach 1 mV, and duration may exceed 10 ms (10 to 100 ms). Vertical divisions are 200 µV, and horizontal divisions 10 ms. (Lower right box shows isolated fibrillation potential with horizontal divisions at 5 ms).

muscular causes of vocal fold immobility. If the cause is neurologic, EMG can localize the lesion to a specific site and indicate whether the upper or lower motor neurons are involved.[10-13] Furthermore, the electrical patterns observed can indicate whether a muscle is innervated, denervated, or undergoing reinnervation, providing valuable prognostic information.[12,14] Previous studies have shown that the innervated or reinnervated immobile vocal fold is more likely to recover motility than a denervated fold. Laryngeal EMG, however, is limited by its expense, invasiveness, and technical difficulty.

Fex and Elmqvist[8] in 1973 correlated EMG with stroboscopic findings in 16 patients with paralyzed vocal folds. Without exception, the mucosal wave was absent in all cases of denervation, and the return of the wave always correlated with reinnervation. As we had observed isolated cases that did not fit this pattern, we reviewed our experience with these studies in patients with immobilized vocal folds.

SUBJECTS

The records of patients referred, between 1989 and 1991, to the University of Washington otolaryngology–head and neck surgery clinic and The Johns Hopkins Hospital otolaryngology–head and neck surgery clinic for suspected vocal fold paralysis were reviewed. Included in the study were those patients with immobile vocal folds who had received both stroboscopy and EMG as part of their evaluation. Of a group of 50 patients with immobile vocal folds, 20 patients received both EMG and stroboscopy, and all

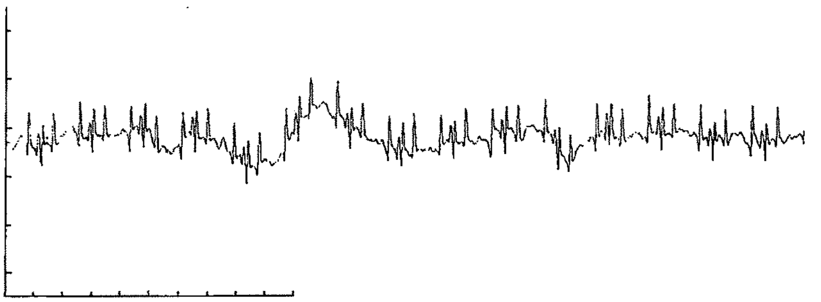

Fig 2. Complex, repetitive discharges recorded at rest from left thyroarytenoid muscle in patient with chronic denervation. These discharges are usually seen in chronic lesions and represent ephaptic transmission between muscle fibers in manner similar to that seen in some cardiac arrhythmias (circular reentry phenomenon). They can be distinguished from other discharges by lack of voluntary control; sudden onset and cessation; and uniform amplitude and frequency (typically 3 to 40 Hz). Vertical divisions are 100 µV, and horizontal divisions 10 ms.

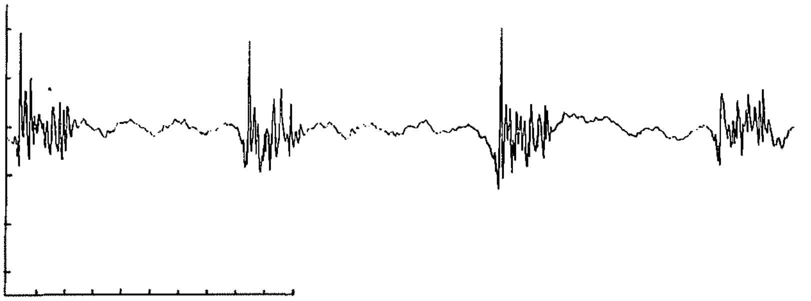

Fig 3. Voluntary motor unit action potentials recorded from left cricothyroid muscle in patient with recent reinnervation. Note that these potentials are very polyphasic and of long duration (>20 ms), consistent with recent reinnervation by axonal sprouting. Instability of motor unit potential is also seen (morphology of each discharge is slightly different), indicating that some of newly formed neuromuscular junctions are unstable. Vertical divisions are 200 μV, and horizontal divisions 10 ms.

20 patients met diagnostic criteria for vocal fold paralysis on the basis of these studies. Nineteen patients were managed surgically with medialization thyroplasty.

METHODS

Surgical medialization is performed, under local anesthesia, through a window in the thyroid lamina at the level of the vocal fold as previously described by Isshiki et al[15] and modified by the authors (P.W.F. and C.W.C.).[16] With the patient in the supine position and prepared for a sterile procedure, a paramedian horizontal incision is used to expose the thyroid lamina while leaving the outer perichondrium intact. A single large skin hook is implanted in the anterior-superior aspect of the contralateral ala and retracted laterally to provide exposure of the ipsilateral lamina. The perichondrium is scored with electrocautery applied to a window template placed 5 to 10 mm posterior to the ventral midline, with the superior edge at the level of the vocal fold. The outer perichondrium is incised and elevated off the window. Cartilage and osteoid material are removed precisely from the fenestra. Care is taken to preserve the inner perichondrium, which is elevated in circumferential fashion off the thyroid lamina with a modified No. 4 Penfield elevator. One of 4 sizing prosthesis templates (3 to 6 mm) is inserted through the window to determine the appropriate size and position of the implant. The implant is then inserted and secured with the appropriate shim. Both implant and shim are prefabricated from dense hydroxylapatite. The wound is then irrigated with antibiotic solution and closed with a 1/4-in Penrose drain placed deep to the strap muscles and brought out through the incision.

Stroboscopy is performed with a Nagashima 70° rigid fiberoptic scope or a Pentax FNL-13S flexible fiberoptic scope mated to a laryngostroboscope (Nagashima LS-3A). The stroboscope is triggered by the subject's fundamental voice frequency in the standard fashion. Recordings are obtained during vowel production (/i/ and /a/) in chest register, head register, and falsetto. Trials were obtained at both minimum and maximum loudness levels. Stroboscopic results are recorded on 3/4-in videotape and analyzed by the investigators at a later date. The investigators were not blinded to the subjects' identities. The presence or absence of the mucosal wave, wave amplitude, wave phase, and glottic closure are evaluated.

The EMG was performed by 2 of the coauthors (P.W.F. and L.R.R.). A percutaneous approach through the cricothyroid membrane using 37-mm, 26-gauge, Teflon-coated monopolar electrodes is employed. A reference electrode is placed over the clavicle, and a ground over the chest. All patients are studied in the awake state. Recordings are obtained from the cricothyroid muscle and the thyroarytenoid or lateral cricoarytenoid muscle. Samples are taken at rest and during sustained vowel production /i/ at low intensity (in chest register) and high intensity (in head register or falsetto) for maximal recruitment. The needle is repositioned for 3 separate site recordings in each muscle.

The EMGs were interpreted by 1 of the authors (L.R.R.). Denervation is determined to be present when absence of voluntary motor unit action potentials, fibrillation potentials, positive sharp waves, or isolated complex repetitive discharges are recorded

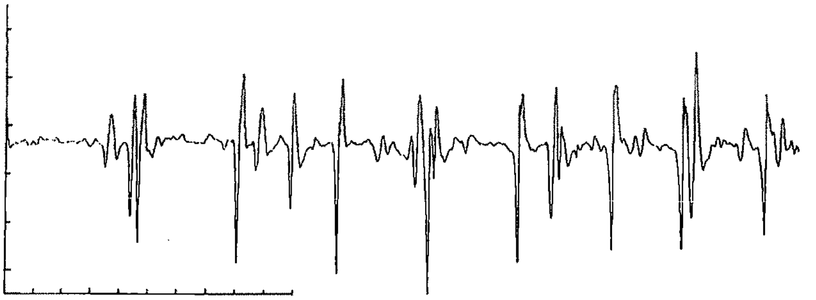

Fig 4. Very large voluntary motor unit action potentials from left thyroarytenoid muscle in patient with old nerve lesion and subsequent reinnervation. Dramatically enlarged motor unit action potentials indicate that muscle fiber territory of each motor unit has been expanded by axon sprouting. Note that vertical divisions are 1,000 μV, and horizontal divisions 10 ms.

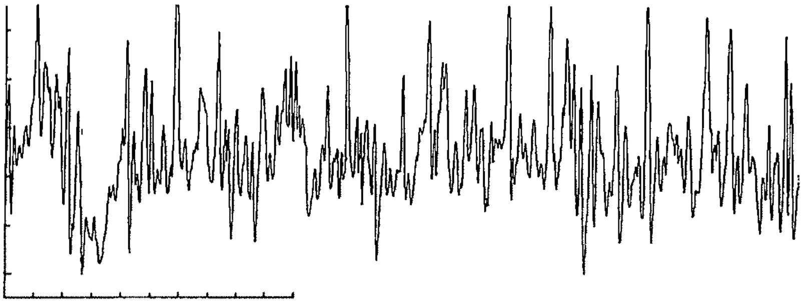

Fig 5. Full interference pattern recorded during high-pitched vowel production /i/ from neurologically intact right cricothyroid muscle. Vertical divisions are 100 μV, and horizontal divisions 10 ms.

on the EMG (Figs 1 and 2). Reinnervation is diagnosed when polyphasic waves and/or partial interference patterns are observed, with or without denervation potentials (Figs 3 and 4). A normal interference pattern obtained during maximal recruitment, combined with a lack of the abnormal patterns noted above, is judged consistent with normal innervation (Fig 5).

The Fisher exact test of probability of distribution in a 2 × 2 contingency table was used for statistical analysis. This test was chosen because it applies to groups with small numbers. Comparisons were made between status of innervation (denervated or reinnervated by EMG criteria) and presence or absence of a mucosal wave on the involved vocal fold. Glottic closure, periodicity, and phase were not used for analysis.

RESULTS

Data from the 20 patients are summarized in Table 1. There were 6 women and 14 men with a mean age of 52 years and a range of 24 to 76 years. Surgical injury to the recurrent laryngeal nerve was the most common diagnosis (10 patients). Other diagnoses included idiopathic causes (5), trauma (2), neoplasm (2), and cerebrovascular accident (1). In 15 patients vocal fold immobility had been present for at least 1 year. Only 1 patient had a disorder of less than 8 weeks' duration. In general, the disorders present in this group of patients were long-standing and stable.

The relationship of innervation status to the presence of a mucosal wave is demonstrated in Table 2. Ten patients were innervated by EMG criteria; that is, the EMG patterns were consistent with normal innervation or reinnervation. Eight of the 10 had mucosal waves present bilaterally, although all of these patients had either incomplete glottic closure involving the posterior membranous portion of the fold or phase shift. The other 2 patients had incomplete glottic closure along the entire length of the vocal fold and aperiodic movement of the involved fold. All 10 patients subsequently underwent medialization thyroplasty. Complete glottic closure was obtained in all patients postoperatively, with return of the mucosal wave in the 2 patients with preoperative aperiodic movement.

TABLE 1. PATIENT DATA

Patient	*Age*	*Sex*	*Diagnosis*	*Duration (wk)*	*Mucosal Wave*	*EMG Result*
1	27	M	Idiopathic	>52	Present	Reinnervated
2	40	M	Surgery	>52	Absent	Denervated
3	24	M	Trauma	12	Absent	Denervated
4	59	M	Idiopathic	>52	Present	Innervated
5	29	M	Neoplasm	>52	Absent	Denervated
6	50	F	Surgery	>52	Present	Reinnervated
7	70	M	Idiopathic	>52	Present	Innervated
8	67	M	Surgery	45	Present	Denervated
9	26	F	Surgery	>52	Present	Reinnervated
10	68	M	Trauma	>52	Present	Reinnervated
11	73	F	Idiopathic	>52	Present	Innervated
12	31	F	Neoplasm	>52	Present	Denervated
13	70	M	Surgery	8	Absent	Denervated
14	31	M	Surgery	>52	Absent	Denervated
15	34	F	Surgery	>52	Present	Reinnervated
16	76	F	Idiopathic	>52	Present	Denervated
17	73	M	CVA	4	Absent	Denervated
18	76	M	Surgery	12	Absent	Reinnervated
19	67	M	Surgery	>52	Absent	Denervated
20	58	M	Surgery	>52	Absent	Reinnervated

CVA — cerebrovascular accident.

TABLE 2. COMPARISON OF PREOPERATIVE FINDINGS OF ELECTROMYOGRAPHY VERSUS STROBOSCOPY

	Stroboscopy	
Electromyography	*Wave Present*	*Wave Absent*
Innervated	8	2
Denervated	3	7

By Fisher's exact test, probability that distribution demonstrated is due strictly to chance is .030.

Ten patients met the EMG criteria for denervation. Three of the 10 denervated patients had normal mucosal waves, with complete glottic closure during phonation. One patient had a stable high vagal injury from a resected glomus tumor. The second patient had an old (45-week) injury to his recurrent nerve, occurring after thyroidectomy, and had previously undergone medialization thyroplasty prior to this study. The third patient's paralysis was idiopathic and long-standing. Electromyography demonstrated electrical silence in the thyroarytenoid and/or lateral cricoarytenoid muscle, and a normal interference pattern in the cricothyroid muscle.

Of the 7 denervated patients with absent waves, 6 underwent thyroplasty with vocal fold medialization during the course of the study. Stroboscopy and EMG were performed immediately before the procedure, and stroboscopy was repeated within 1 week after the procedure and at 1 month and 6 months. Preoperative stroboscopy revealed incomplete glottic closure along the entire length of the vocal fold in all 6 patients. These 6 patients developed mucosal waves with complete glottic closure after thyroplasty despite no expected change in their status of innervation (Fig 6). Phase shift was present in 4 of these 6 patients postoperatively.

By the Fisher exact test, the probability that the distribution demonstrated in Table 2 is due strictly to chance is .030. The distribution obtained when the postoperative stroboscopy results are used is demonstrated in Table 3. The association between status of innervation and the presence of the mucosal wave exhibited in Table 2 no longer holds. The probability of random distribution in Table 3 is .50.

DISCUSSION

Our data support the contention that the mucosal wave is reliably present in the innervated vocal fold. This has been described previously.[1,2,17] However, our findings suggest that the status of innervation is not the sole determinant of the presence or absence of the mucosal wave. Three patients in our preoperative group and 9 patients in the postoperative group had mucosal waves despite EMG-proven denervation. That a mucosal wave may be present in a denervated state is supported by studies in excised canine and human larynges in which, under the proper conditions of cord tension, glottic aperture, and transglottic airflow, a mucosal wave could be demonstrated by high-speed photography.[18]

The Isshiki (type I) thyroplasty has been shown previously to improve the quality of the mucosal wave in paralyzed vocal folds in which the status of innervation was not determined.[19] The Isshiki procedure medializes the immobile vocal fold, improves

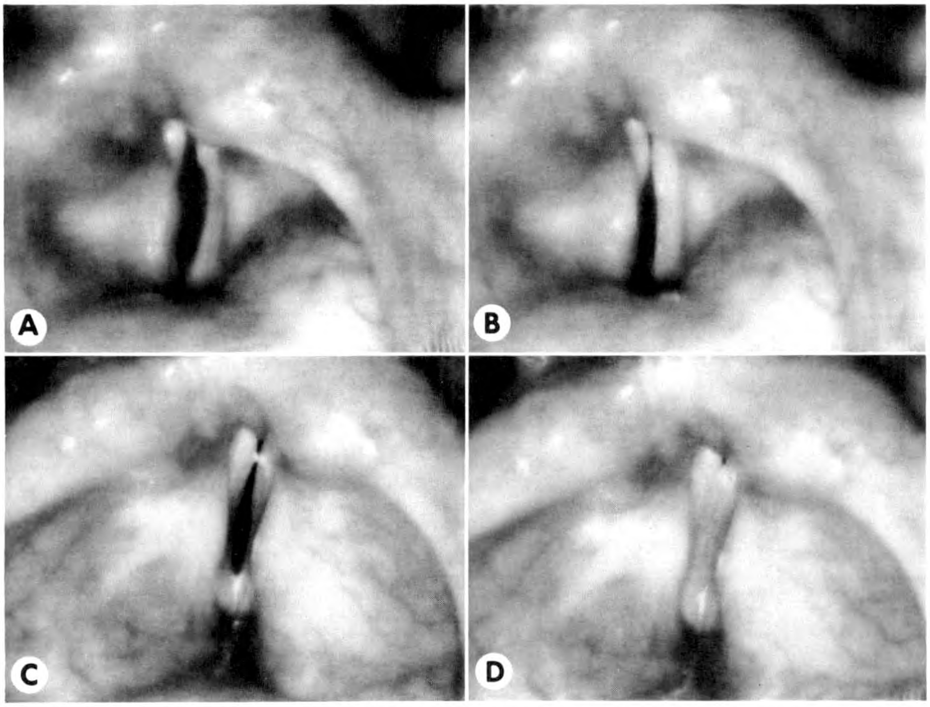

Fig 6. A,B) Preoperative stroboscopic examination in patient with long-standing idiopathic vocal fold paralysis and electromyography demonstrated electrical silence in thyroarytenoid and lateral cricoarytenoid muscles. Complete glottic gap and large-amplitude, aperiodic mucosal waves are present during phonation. C,D) Following medialization thyroplasty, stroboscopic examination reveals complete glottic closure and symmetric mucosal waves with normal periodicity.

TABLE 3. COMPARISON OF FINDINGS, AFTER MEDIALIZATION THYROPLASTY, OF ELECTROMYOGRAPHY VERSUS STROBOSCOPY

	Stroboscopy	
Electromyography	*Wave Present*	*Wave Absent*
Innervated	10	0
Denervated	9	1

By Fisher's exact test, probability that distribution demonstrated is due strictly to chance is .50.

glottic closure during phonation, and may change the tension of the vocal fold.[20] Thus, the mucosal wave can be present when there is normal, supple mucosa, adequate transglottic airflow, appropriate vocal fold tension, and glottic closure during phonation.[21] This suggests that the status of innervation affects the mucosal wave only when it can impact one of these factors. However, the configuration of the phonatory mechanism can be adjusted such that a mucosal wave and improved phonation can exist despite lack of innervation.

Whether or not the addition of a reinnervation procedure to static medialization improves the outcome in patients with unilateral vocal fold paralysis remains to be answered. Theoretically, a combined procedure will medialize the vocal fold, improve muscle tone, and add dynamic control of vocal fold tension.[22] These latter effects would be expected to improve pitch control and minimize the phase shift observed in our patients following adequate medialization. Further study with objective assessment of voice quality is necessary to evaluate outcome following thyroplasty versus thyroplasty combined with a reinnervation procedure.

CONCLUSIONS

Stroboscopy and EMG are complementary studies that provide different information: the former provides a dynamic picture of vocal fold function, while the latter assesses neuromuscular integrity. One cannot replace the other. While the prognostic information available from EMG has been well defined, the prognostic value of stroboscopy remains to be determined. The presence of a mucosal wave does not necessarily correlate with the status of innervation; and, while the status of innervation may affect vocal fold position, muscle tone, and glottic closure, it is not the sole determinant of the mucosal wave.

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TEMPORARY NASOSINUSAL DRAINAGE AND LAVAGE IN CHRONIC MAXILLARY SINUSITIS

STATISTICAL STUDY ON 847 MAXILLARY SINUSES

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We report on 498 patients suffering from chronic maxillary sinusitis verified by sinusoscopy through the inferior meatus and by computed tomography of the sinuses, which permitted also the diagnosis of coexisting chronic ethmoidal sinusitis. The patients were treated by temporary drainage through a polyethylene drain tube left in place at the end of the antroscopy for daily lavage with saline solution and daily instillation in the sinus of thiamphenicol glycinate hydrochloride (similar to chloramphenicol) and *N*-acetyl-L-cysteine. We followed up 847 maxillary sinuses during the lavages according to 2 parameters: 1) recovery of a clean washout product at the macroscopic examination and 2) recovery of normal ostial patency as measured by sinusomanometry. We concluded that 1) the association with ethmoidal sinusitis does not significantly modify the treatment duration, and 2) fewer than 4% of the maxillary sinuses are likely to recover normal parameters after the 23rd day of lavage, and it is therefore useless to continue this treatment much longer. Of the maxillary sinuses, 36.25% were not submitted to any surgery. The results gained by the lavage technique have to be protected from recurrence by the treatment of general, focal, or local causes.

KEY WORDS — chronic maxillary sinusitis, sinusomanometry, temporary drainage.

INTRODUCTION

The first technique of puncturing the maxillary sinus for drainage was reported by Jourdain in 1776 (cited in Willemot and Michel[1]). Since that time many authors have developed techniques with temporary drain tubes to avoid recurrent puncture of the maxillary sinus, already a source of discomfort to the patient.[2] This work aims at defining statistically the usefulness of temporary drainage with daily lavage and local antibiotic instillation in cases of chronic maxillary sinusitis. It also aims at defining time limits for this kind of treatment, weighing on one side the benefits that can be expected from cleaning the antral cavity, providing the mucosa with oxygen, and enabling the ostium to recover a normal patency, and on the other side the inconveniences and secondary effects of lavage and the drain itself.

In some cases, a tube made of polyethylene may even act as a foreign body, and moreover it may function as a gateway to the sinus for selected bacterial and mycotic infections, especially when antibiotics are injected through the tube for long periods of time. This temporary drainage and lavage technique must be followed by functional microsurgery and ethmoidectomy when necessary.[3-6]

MATERIAL AND METHOD

This work started with a pool of 557 patients. All were suffering from chronic maxillary sinusitis defined as being symptomatic, lasting for at least 3 months, and being resistant to well-conducted medical treatment. Cases of nasal polyposis were excluded. These patients underwent maxillary sinuscopy (Wolf Panoview 30° and 70°), frontal sinuscopy

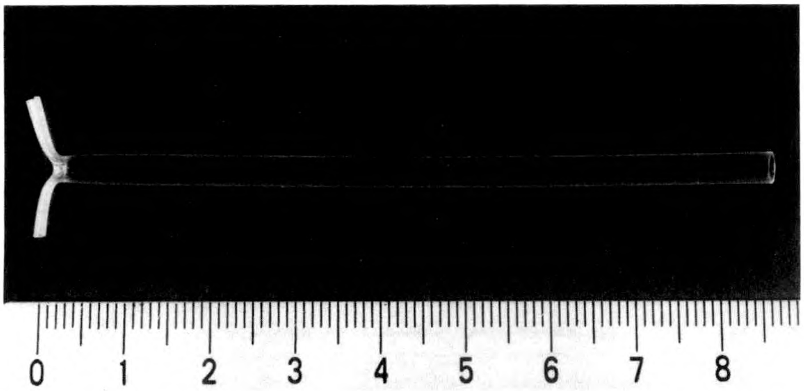

Fig 1. Polyethylene drain tube designed to be put through sleeve (Wolf) after sinus endoscopy. Inner diameter of sleeve is 4 mm. Outer diameter of drain is 3.7 mm. Scale is in centimeters.

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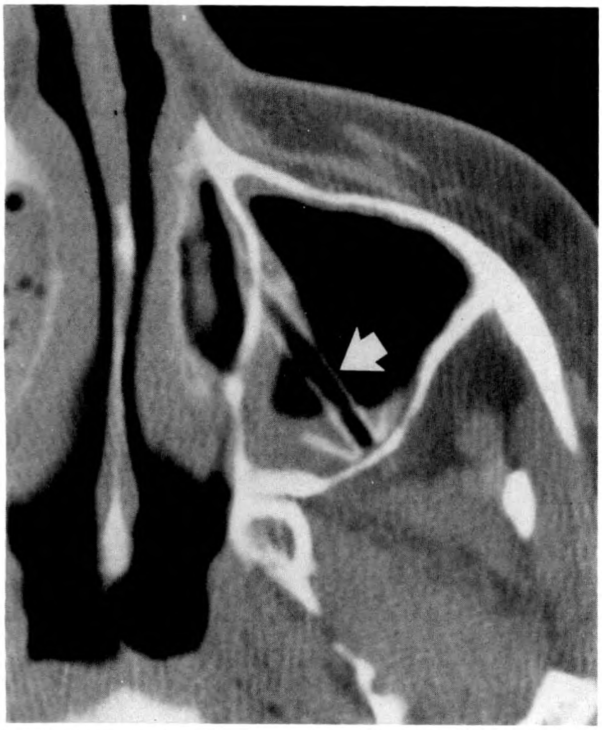

Fig 2. Computed tomogram of maxillary sinuses. Drain is in place (arrow). Incidence of CT slice does not allow outer end of tube in nasal fossae to be shown.

when necessary, and computed tomography (CT) of the sinuses (Siemens, Somaton, 4-mm thin coronal sections), from which the diagnosis of an associated chronic ethmoidal sinusitis can be made.[7] The maxillary sinus endoscopy was performed under local anesthesia, through the inferior meatus, according to Terrier's technique.[8] A 4-mm polyethylene drain, terminating in small unfolding wings (Fig 1), was put in place in the maxillary sinus (Fig 2) at the end of the medical examination if a dyspermeable ostium and/or infected antral smears were found. Sinusomanometry, in a simplified version of the Drettner technique,[9-11] was performed during antroscopy and then in follow-up twice a week at the hospital. Daily lavages were performed, either by the general practitioner, or by ourselves on the days of sinusomanometry follow-up.

The results were divided into 2 groups: 1) normal patency of the ostium and 2) nonpatency of the ostium, including internal valves, external valves, and both internal and external ones. So that sinusomanometry would not be influenced by an accessory ostium giving false-positive results, the "normal" sinusomanometries (including patent natural ostia and accessory ostia) were excluded from the curves analyzing ostial patency. The lavages were made with 250 mL of a sterile saline solution (sodium chloride 9%) and were immediately followed by the instillation through the drain of 750 mg thiamphenicol and 300 mg *N*-acetyl-L-cysteine until a clear washout product was obtained from the sinus at the macroscopic examination, and until the sinusomanometry results were normal. A clear washout product was chosen as the sign of a low-infected or noninfected maxillary mucosa. Under the conditions of this study, normal sinusomanometry results reflect a patent ostium. The role of an occluded ostium is well known in the pathogenesis of maxillary sinusitis.[12]

Fifty-nine patients left the study: 5 left for personal reasons, 14 were excluded because of a missing CT scan, 19 were very young and not compliant to the treatment, 4 patients were followed up by other physicians, and 17 left the study for other reasons. The final material was therefore reduced to 498 patients, meaning 885 drains comprising 847 maxillary and 38 frontal drains. Figure 3 shows the distribution of ages and sexes, which is very similar to that of other studies. The peak (modal) age was between 30 and 40 years.

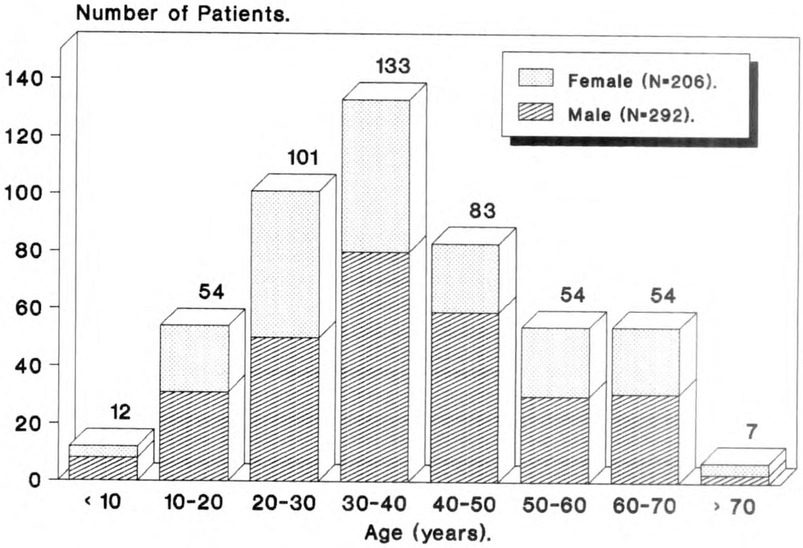

Fig 3. Breakdown of patients by sex and age (N = 498).

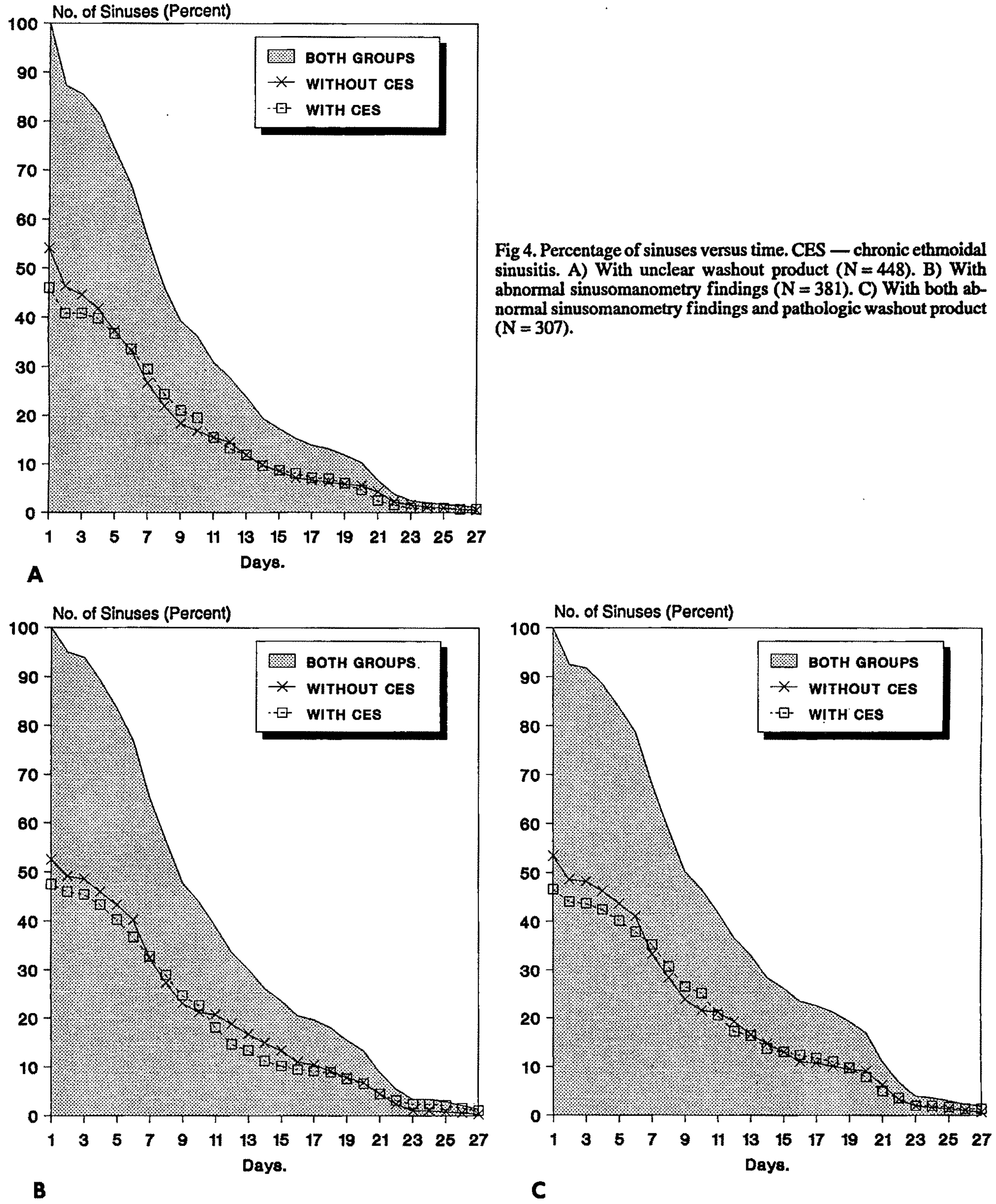

Fig 4. Percentage of sinuses versus time. CES — chronic ethmoidal sinusitis. A) With unclear washout product (N = 448). B) With abnormal sinusomanometry findings (N = 381). C) With both abnormal sinusomanometry findings and pathologic washout product (N = 307).

COMPLICATIONS

During the treatment few complications were noted. There were 3 cases of subcutaneous facial and palpebral emphysema during the lavage procedure, and 4 cases of nose bleeding requiring nasal packing for 2 days. Four frontal drains and 127 maxillary drains were lost and replaced.

RESULTS AND DISCUSSION

Figure 4A shows the decreasing curve of the percentage of maxillary sinuses remaining with an unclear washout product (N = 448 sides). The x-axis

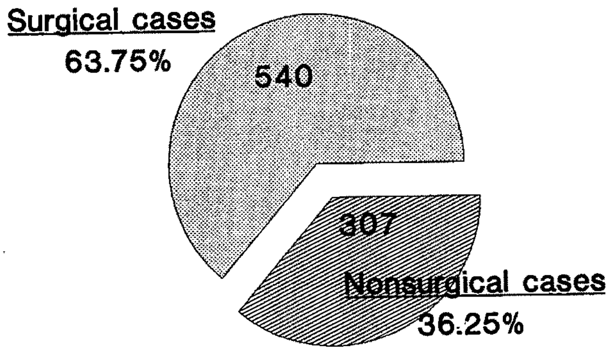

Fig 5. Distribution of nonsurgical and surgical (middle meatus antrostomy and Caldwell-Luc procedure) maxillary sinuses, after temporary drainage and lavage.

shows the days of treatment. Figure 4B shows the decreasing curve of the maxillary sinuses remaining in treatment that were abnormal on sinusomanometry (N = 381). Figure 4A,B also presents the percentages of maxillary sinuses with or without associated ethmoidal sinusitis. Both the ethmoidal curves (with or without ethmoidal sinusitis) decrease the same way without any significant difference. This statement regards only the behavior of the curves and does not contradict the major role played by ethmoidal sinusitis as 1 of the causes of maxillary ostium occlusion, which in turn may generate maxillary sinusitis.[6] Two reasons can be proposed to explain this unexpected behavior of the curves. First, this phenomenon can be attributed to the fact that the drain tube is supplying the maxillary sinus with oxygen and so minimizes the role of an occluded maxillary ostium potentially involved with ethmoidal sinusitis. Second, the ethmoidal disease may have been cured or improved by the lavage technique. Further study is needed to clarify this point.

In regard to the quality of the washout product, the hypothesis according to which ethmoidal smears could possibly contaminate washout product is not confirmed.

The shaded surfaces showing the 2 groups (with and without ethmoidal sinusitis) in Fig 4A,B decrease equally, indicating that the changes occurring in sinusomanometry and in the quality of washout product seem to be linked together during the lavages.

The 2 curves (Fig 4A,B) turn quite asymptotic after the 23rd day of treatment. Beyond 23 days, fewer than 4% of the sinuses are expected to recover normal ostial patency or a clear washout. So 307 sinuses can be grouped under a single curve (Fig 4C) according to the 2 conditions for a healthy maxillary sinus: a normal ostial patency and a clean antral cavity. These 307 maxillary sinuses represent 36.25% of all the samples and did not have to be operated on at the end of the lavages (Fig 5).

Figure 4C shows again that the 2 curves related to the ethmoidal situation can almost be superposed. The same possible causes may be invoked to explain these findings as for Fig 4A,B.

The shaded area summarizing the total number of the maxillary sinuses remaining in treatment decreases after each lavage. This curve also becomes asymptotic after the 23rd day; that is when fewer than 4% of the maxillary sinuses can be expected to recover. The mean duration of the treatment was about 9 days.

CONCLUSION

The declining curves from day to day along the lavages indicate that the more the maxillary sinus is washed, the more normalized parameters can be expected. But there seems to be a time limit to this treatment, because of the fact that the curves turn asymptotic after the 23rd day. This asymptotic behavior enables us to conclude that it is useless to perform lavage and drainage for more than 23 days because of the very low recovery rate (fewer than 4% of the cases) that can be expected after that time. During the fourth week of treatment lavages can be stopped, the drains can be removed, and a decision can be made for functional microsurgery (middle meatotomy) or for the much less frequent conventional radical surgery (Caldwell-Luc).

As far as the advantages of lavage are concerned, a little more than 36% of the maxillary sinuses achieved nonsurgical status by recovering a patent natural ostium and a clean cavity. But it is important to point out that recovering a patent ostium and a noninfected mucosal status only means that the maxillary sinus is in good shape again, and does not exclude further treatment of local or systemic causes when indicated.

In cases of chronic ethmoidal sinusitis, partial or total ethmoidectomy is to be done in order to avoid early recurrences. Functional microscopic or endoscopic surgery must be performed to free the middle meatus if it appears to be necessary. Focal causes such as dentogenic ones or septal deviations must be treated. Systemic causes (eg, allergy, immune deficiency) have to be recognized and treated.

Moreover, even when the lavage technique has failed to restore normal patency and a clean antral cavity, surgery is easier to carry out and entails less surgical risk, thanks to a less infected middle meatus and decreased perioperative bleeding due to reduced local inflammation. The disadvantages of lavage are that it is obviously time-consuming, rather expensive, and very difficult to conduct in young children.

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CLINICAL APPLICATIONS OF VESTIBULAR SCIENCE

The conference Clinical Applications of Vestibular Science will be held in Los Angeles, California, February 12-13, 1994. For information, contact Marjorie Harris, Program Coordinator, 15-50 Rehabilitation Center, UCLA, Los Angeles, CA 90024-1651; telephone (310) 825-5131; fax (310) 206-2327.

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FOURTH INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON INNER EAR MEDICINE AND SURGERY

The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone (303) 788-4320 or (303) 850-9545; fax (303) 788-4234.

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ESOPHAGEAL STRICTURE: AN UNCOMMON COMPLICATION OF FOREIGN BODIES

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Ingestion of foreign bodies is common in infants. As a rule, the infant is being observed and the event is witnessed. When it is unwitnessed, acute symptoms bring the problem to the attention of a physician. When the ingestion is not witnessed or symptomatic, its presence can only be surmised. The object can create injuries and chronic symptoms that are not typical for this accident. Here is reported an ingestion of a coin that went undiagnosed and untreated for more than a year. The result was a transmural esophageal injury with stricture formation. The diagnostic methods and transcervical repair are described.

KEY WORDS — esophagus, foreign body, stricture.

INTRODUCTION

The ingestion of foreign bodies is a common event in the pediatric population, especially in the young age group.[1,2] Often the event is observed, but may not be, and the physician is not alerted to the possibility. He or she is then left to interpret the myriad of symptoms, including coughing, drooling, dysphagia, respiratory distress, and cyanosis. Acute perforations are often the result of a sharp foreign body.[3,4] These cause immediate symptoms, and treatment is not usually delayed. The injury may not be acutely symptomatic and the foreign body goes unnoticed until a complication occurs. A blunt object can exist for some time before damage to the esophagus occurs. Those that do not pass through to the stomach cause a chronic inflammation, and several cases of migration into the mediastinum have been reported.[5]

Here a case is reported of a coin ingestion that was not witnessed and went undiagnosed for 1 year. This resulted in chronic local inflammation and, eventually, a stricture obstructing the esophagus.

CASE REPORT

A 1-year-old girl developed symptoms of congestions, vomiting, and coughing. There was no history of trauma, acute infection, or ingestion of a foreign body. Allergies were considered likely because of a strong family history. For the next 8 months she underwent dietary changes eliminating dairy products, with some improvement. At 22 months of age the emesis worsened and she began having wheezing, fever, and insomnia. At this point, a chest radiograph was obtained that revealed a foreign body in the upper esophagus (Fig 1A). The child underwent esophagoscopy and extraction of the foreign body (a copper penny). The operative report records the extraction of a corroded penny. The esophagus was described as bloody and inflamed. Esophagoscopy past this point was deferred to avoid injury.

She was not followed up for over 1 year for unclear reasons. Then, at age 4, when she could only tolerate liquids and was vomiting all solid foods, an esophagogram was obtained (Fig 1B). A tight esophageal stricture with a small diverticulum was diagnosed. At that time, transthoracic resection of the esophagus was recommended. The family refused. The child was seen sporadically by several physicians over the next 2 years, but consent for treatment was never given.

At age 6 she came under our care with the above history. Physical examination revealed a small (17 kg) but otherwise healthy and alert young girl. The head and neck examination findings were normal, the chest was clear, and the abdomen was normal. The barium swallow study was reviewed.

She underwent endoscopic evaluation, which demonstrated a stricture at the level of the cervical esophagus. Only a 4F catheter could be passed. The child underwent repair of the stricture through a right-sided transcervical approach. The findings at the operation revealed a small pseudodiverticulum, a tight stenosis, and a large, dilated proximal esophagus. There was a dense inflammatory reaction and scar around the esophagus. The trachea was not involved. An esophagoplasty was performed without esophageal resection. This allowed the stricture to be repaired without the risk of tracheal or recurrent laryngeal nerve injury (Fig 2). In the 3 months fol-

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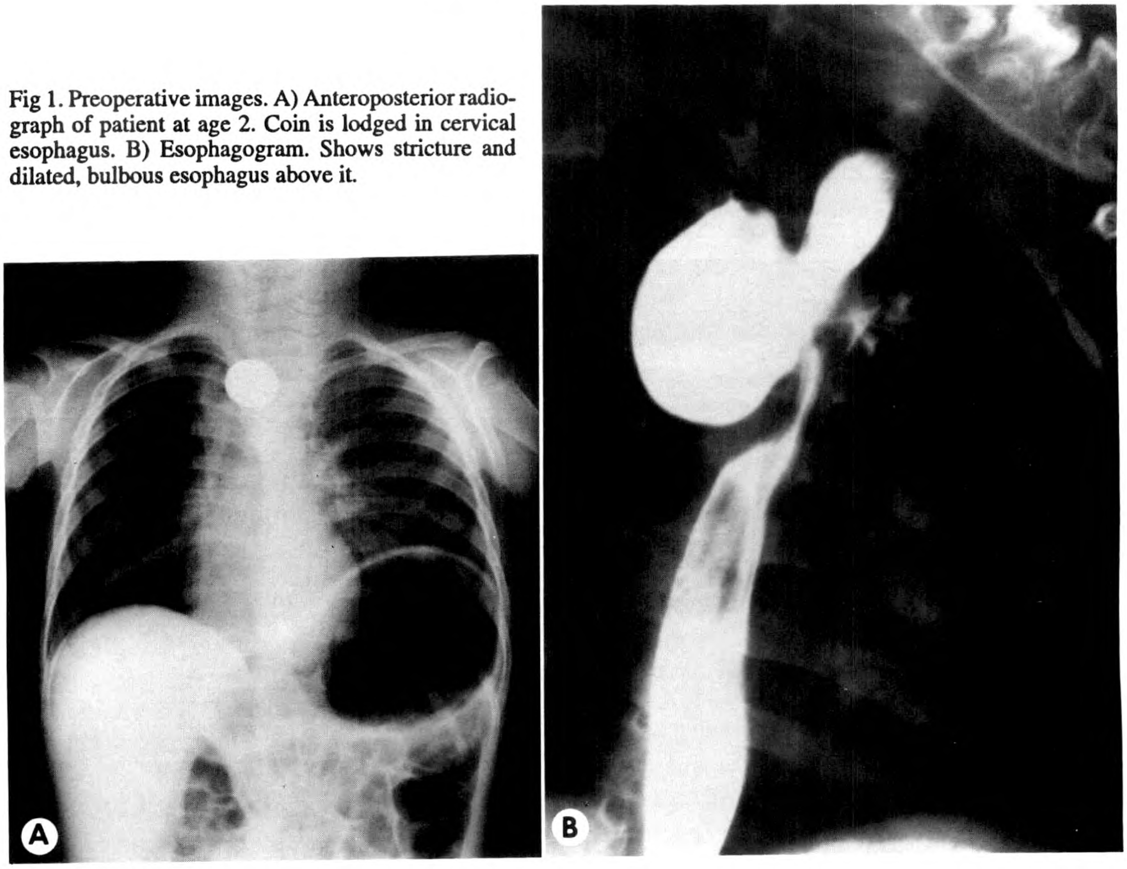

Fig 1. Preoperative images. A) Anteroposterior radiograph of patient at age 2. Coin is lodged in cervical esophagus. B) Esophagogram. Shows stricture and dilated, bulbous esophagus above it.

lowing, she underwent 2 esophageal dilations.

Three months after the procedure she was tolerating liquids well. An esophagogram showed a patent esophagus with some deformity (Fig 3A). She was placed on a regular diet and tolerated this with no choking, dysphagia, or emesis. She continued to be asymptomatic, and a surveillance barium swallow study was done at 18 months (Fig 3B). Findings were normal. She was seen again 2 years after surgery. Her weight had become normal (23 kg) and she had no deglutition problems with liquids or solids.

DISCUSSION

This case illustrates 2 unusual and controversial points. First, the chronic presence of an esophageal foreign body is unusual, since these are generally removed soon after the ingestion. Second, the complication of an esophageal stricture in the cervical esophagus is rare, especially one due to a blunt foreign body.

When a child ingests a foreign body, a witnessed choking episode is common (80%). Either a choking episode or some subsequent problem brings the child to medical attention. Holinger[6] reported in his review that 95% of foreign bodies have been present for less than 3 months when they are diagnosed, and only 1% are present more than 6 months. This underlines the concept that the diagnosis of foreign body ingestion must be suspect, even when the symptoms are subtle and no definite history is attainable.[7]

The suspicion of an object in the esophagus can elude the physician if the symptoms are mild or if the object is difficult to image. A small, smooth object such as a coin or bingo chip may be asymptomatic for some time. Occasionally the object is identified accidentally when radiographs are being obtained for other reasons. However, some foreign bodies, such as toy parts, are not radiopaque and cannot be demonstrated radiologically even with a contrast study.[8,9] Even when symptoms are present, certain objects defy detection by techniques commonly used in the emergency department. Xerography[10] may be helpful at times, especially when tomographic techniques are employed. If obstruction and perforation do not exist, either esophagitis or migration will alert the physician over the first few weeks. After this, a complication of the esophageal injury such as stricture, fistula, or vascular injury will cause delayed symptoms such as dysphagia, cough, or hemorrhage.[5,11-13]

The inaccuracy of all these techniques makes noninvasive diagnosis difficult. For this reason endoscopy remains the most effective diagnostic technique.[4] This also offers the best therapeutic approach

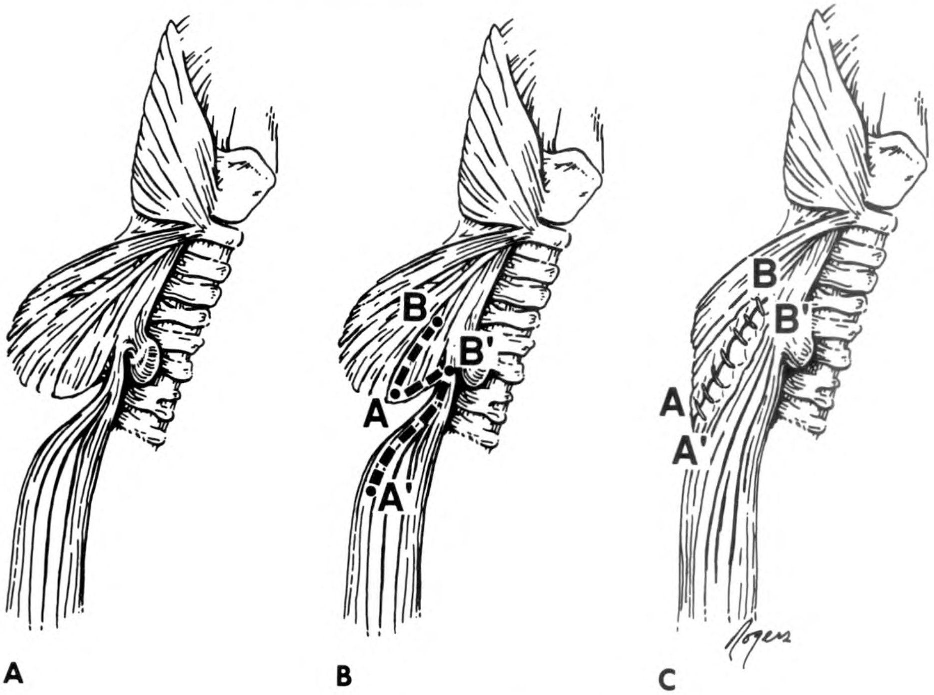

Fig 2. Composite drawing of operation. A) Proximal esophagus was dilated, and small pseudodiverticulum was identified at area of stricture. B) Incision was made to create esophagoplasty. C) Completed reconstruction. A, A', B, B' — areas of esophageal incision that are apposed for final repair.

in the acute situation.

The cause, location, and severity of this esophageal stricture is unusual. Benign strictures can be described in terms of causation, location, and severity. Strictures of the esophagus may result from esophagitis, caustic ingestion, injury, surgery, or malignancy, or may be congenital. The first step in dealing with this entity is to remove the cause. If a foreign body is present, it needs to be extracted; if gastroesophageal reflux is present, it needs to be resolved.

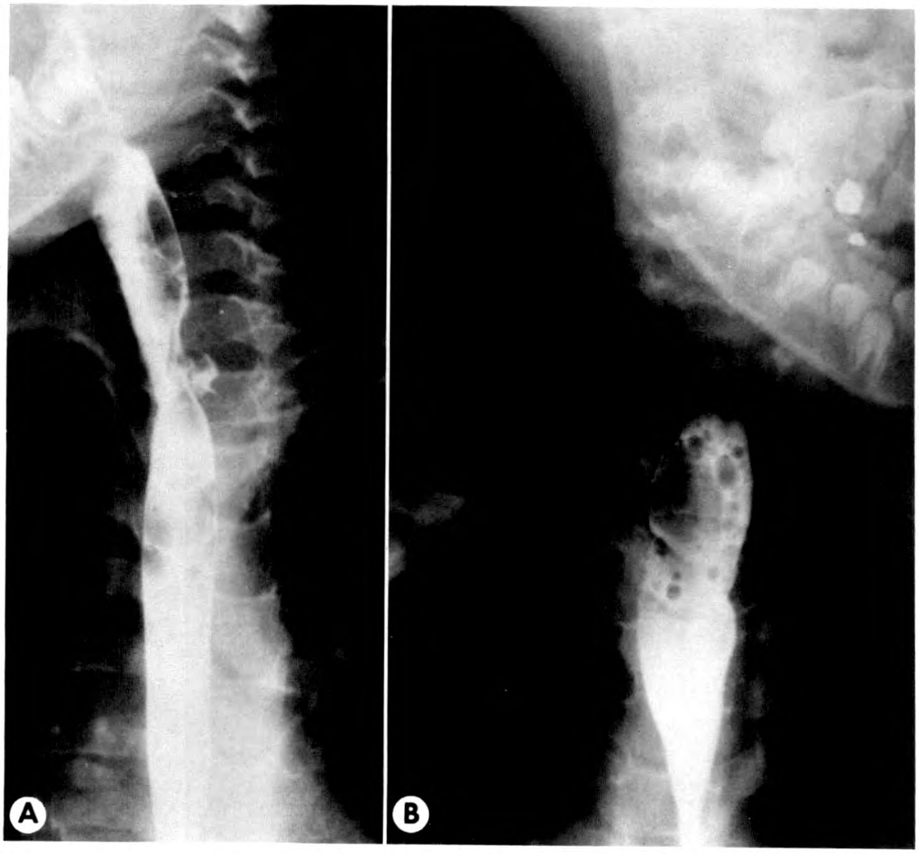

Fig 3. Postoperative esophagograms. A) Three months. Area of anastomosis can still be identified. There is no obstruction. B) Eighteen months. Appearance is normal.

The severity of the stricture and the location will dictate subsequent treatment. Mild stenosis can be dilated with or without the use of adjuvant medication such as steroids and antibiotics.[14-17] When the lesion is too narrow or distorted for safe dilation, then surgical correction may be necessary.[18,19] In our case, the lumen was less than 2 mm in diameter. The long-standing presence of the stricture and rigid scar tissue made dilation a poor option. Also, the distortion and diverticulum made it difficult to pass dilators antegrade without a guide wire. Regardless of the severity of the narrowing, the cause is a key factor in choosing a method of treatment. Endoluminal obstructions respond to endoscopic techniques such as laser ablation or cautery. Transmural disease with a distorted esophagus and an hourglass shape is difficult to treat safely or effectively in this fashion. The risk of perforation and the likelihood of a poor response make endoscopic laser intervention risky.

The level of this stricture was at the thoracic inlet. Our approach was right-sided transcervical. This proved effective. We had excellent control of the esophagus both above and below the stricture. Also, the critical structures of the thoracic outlet (brachial plexus and major vessels) were avoided. The mediastinal inflammation and scarring were extensive and dense. An esophageal resection would have placed the left recurrent laryngeal nerve at unnecessary risk. A flap stricturoplasty (Fig 2) was performed, avoiding those structures adhered to the injured esophagus.

At another location, such as the thoracic esophagus, resection with end-to-end anastomosis is feasible. This is especially true for the distal esophagus, which is not adjacent to major blood vessels or critical nerves.

The long-term recovery was uneventful. The child's serial esophagograms demonstrated the typical changes of recovery from such a repair. The ultimate result was a functionally normal esophagus.

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LIGHTNING INJURY OF THE TYMPANIC MEMBRANE

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A number of cases of otologic injuries by lightning strikes have been described in the otolaryngological literature. The mechanism of these injuries remains uncertain. We report 3 cases of lightning injury that presented to us. Analysis of these cases suggests that the mechanism of injury is direct conduction of electricity from the scalp to the soft tissues of the external auditory canal to the tympanic membrane. The conduits of the electrical surge are the subcutaneous blood vessels, smaller vessels being damaged more than larger vessels. Since the tympanic membrane central vessels are smaller than the canal vessels, the central area of the tympanic membrane would be most vulnerable, and this is seen clinically. A review of the literature supports this proposed mechanism of injury.

KEY WORDS — electricity, lightning, tympanic membrane.

INTRODUCTION

The array of injuries in lightning-damaged ears has been well documented. Large tympanic membrane perforations,[1-5] sensorineural hearing loss,[1-3,6] and disequilibrium[1,3,6] are common findings. Ossicular chain disruption and temporal bone fracture are not seen in these injuries, even in cases of large tympanic membrane perforations.[1-6] The external auditory canal can be burned[1-4] or intact in the presence of tympanic membrane perforation.[4,5]

This consistent configuration of injuries, that soft tissues are injured while bony structures are left intact, has led to speculations about the mechanism of otologic lightning injuries. Proposed mechanisms of injury have been a concussive "blast" effect on the ear,[1,2] a "direct" effect of electrical conduction,[1-4] a "splash" effect,[6] a "cylindrical shock wave of electrons,"[4] and thermal burn.[2,4] We describe 3 cases of lightning injury to the ear that presented to the University of Iowa Department of Otolaryngology–Head and Neck Surgery. In these 3 cases, the character of the tympanic membrane injury, as well as histologic evidence, supports the hypothesis that lightning injures the ear through direct electrical conduction.

CASE REPORTS

Case 1. This 27-year-old farmer awoke on the ground with singed scalp hair and burns on his ankles. On physical examination his face was plethoric, and his right neck had superficial burns. Both external auditory canals were normal. Tympanic membranes consisted of the annulus only. The malleus handle appeared normal bilaterally. An audiogram showed bilateral conductive hearing loss. Nine months later, the right tympanic membrane had healed completely, closing the air-bone gap. The left had healed to a 30% anterior perforation. Anterior myringoplasty through an endaural incision evidenced dense fibrotic tissue directly beneath normal-appearing epithelium of the external auditory canal. Histopathologic examination later confirmed that this was scar tissue (see Figure). Intraoperatively, a flap of membrane was found turned under the anterior tympanic membrane. This segment corresponded exactly in size to the perforation. The tympanic membrane healed well postoperatively.

Case 2. This 46-year-old jogger was resuscitated and intubated on the running track. On initial physical examination, there were burns of the right cheek and neck. The external auditory canals were clear. The right tympanic membrane had a large central perforation. The left was normal. After the patient regained consciousness and began to ambulate, ataxia was noted. An audiogram showed a conductive hearing loss in the right ear. Ice water caloric testing evoked no response in either ear. Four months later he underwent successful myringoplasty in the right ear. The ossicles were noted to be normal.

The patient never recovered vestibular function. He could not remain standing without holding onto support, and he could not ambulate or shower with his eyes closed.

Case 3. This 8-year-old girl was resuscitated on the softball field. Physical examination found singeing of the right parietal area hair, and superficial burns of the right side of the face and neck. Both external auditory canals were normal. The right tympanic membrane had a large perforation. The left was normal. An audiogram showed a conductive hearing loss in the right ear. A computed tomography scan

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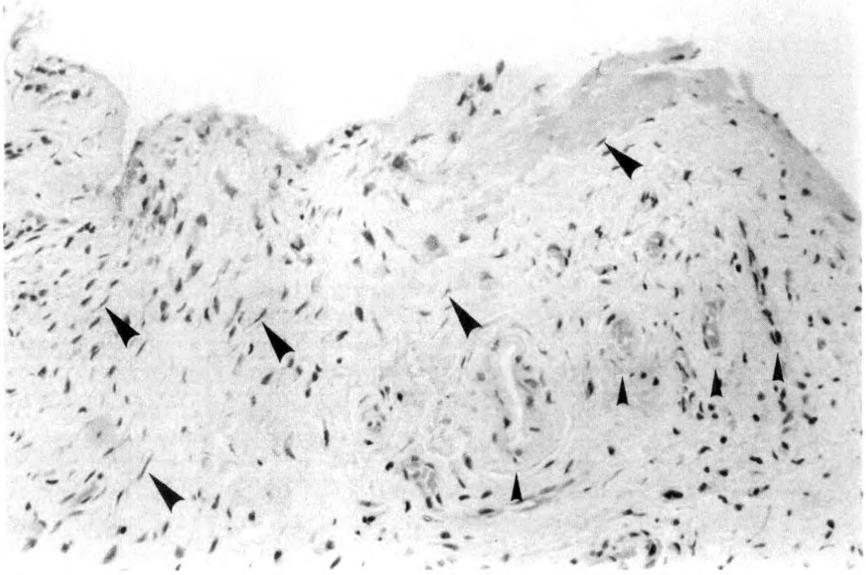

(Case 1) Subcutaneous tissue of external auditory canal (H & E, original ×60). Dermis consists entirely of dense fibrosis, with typical fibroblasts indicated by larger arrowheads. Smaller arrowheads indicate blood vessels coursing through scarred dermis.

showed no evidence of a basilar skull fracture. Myringoplasty was attempted 3 months later, but failed. A second attempt at myringoplasty was successful, but the patient subsequently needed placement of a ventilation tube for persistent effusion. The ossicles were normal on each exploration.

DISCUSSION

The effect of lightning on the tympanic membrane is illustrated in these 3 case reports and in the otologic literature. The tympanic membrane appears to disintegrate in the lightning injury, and to retain unusual powers of regeneration. The tympanic membrane typically disappears in lightning injury, leaving only the ossicles and annulus intact.[1-6] These holotympanic perforations can heal spontaneously.[1,2,4] Among our cases, the first patient's large left perforation healed completely. The right healed to the extent that the turned-under tympanic membrane flap permitted. Our third patient appears by history to have had poor eustachian tube function, which may have hindered her spontaneous healing.

Lightning injures the membranous inner ear, while sparing the bony structures of the middle ear. Evidence of injury to the inner ear membranes and soft tissues is seen clinically as sensorineural hearing loss and vertigo.[1-3] Histopathologically, disruption of the cochlear membranes and blood in the inner ear is seen.[1,6,7] Sensorineural hearing loss and vertigo can be seen even in the face of an intact tympanic membrane.[2,4,6] Our second case illustrates this also, since this patient had no response to ice water calorics even in the ear that had no perforation.

The consistent pattern of lightning injury demonstrates the mechanism of injury. Clearly, the injury caused by lightning is not a concussive ("blast") effect. No bony damage, either to the ossicles or to the temporal bone, is seen either clinically[1-6] or histopathologically.[1,6,7] We also saw no bony injury in our patients, either on exploratory tympanotomy or by radiographic imaging.

The "splash" effect[6] refers to the glancing of the lightning bolt off a nearby object to strike the victim. This term does not elucidate the actual mechanism of injury; it only describes the route of energy transfer external to the victim. The "cylindrical shock wave"[4] mechanism describes the air around the axis of the bolt expanding to burst the tympanic membrane. This is a variation of the "blast" explanation.

Thermal burns have been proposed as a mechanism of injury.[4] While thermal burns of the external canal[1-4] and tympanic membrane[2,4] are seen, they are inconsistent. In addition, as in our 3 cases, the tympanic membrane is often perforated while the external auditory canal appears unscathed.[4,5] It does not seem reasonable that an external source could burn the medial structure, the tympanic membrane, while leaving intact the lateral structure, the external canal. In all, we feel the evidence argues against blast or thermal burn as mechanisms of otologic lightning injury.

Instead, direct flow of electrical energy through the patient is the likely mechanism of lightning injury. Electricity travels along the path of least (electrical) resistance. Human tissues range from most resistant to least resistant in this order: bone, fat, tendon, skin, muscle, blood vessels, and nerves.[8,9] In our 3 cases, and in some of those in the literature,[1] the ear most affected by the lightning strike was the one with facial or hair burns adjacent to it. This finding is suggestive of an entry point of the electrical charge through the electrically resistant cutaneous surface. Further, we have found histologic evidence of subcutaneous energy transfer along the external auditory canal. Our first patient had normal external auditory canals with intact canal skin after the initial injury. However, at operation, dense scar (see Figure) was found beneath the intact epithelium of the external auditory canal. Finally, the disruption of the inner ear membranes seen histologically is consistent with electricity's propensity to travel well in fluid-filled spaces. This all fits with direct electrical energy transfer as the mechanism that explains the findings of otologic lightning injury.

The pathophysiologic pathway by which electrical transfer through soft tissue leads to scar is well described. Electricity is known to pass preferentially through blood vessels,[8,9] and can leave a severe vasoconstriction in its wake.[10] The tissue that has transmitted the charge may appear normal and may only begin to manifest the effects of vasoconstriction days later, when previously "normal" tissue turns gangrenous.[11] These pathophysiologic events probably contributed to scar formation in our first patient.

The mechanism of the characteristic disintegration of the tympanic membrane in lightning injury remains speculative. This disintegration is probably the effect of an electrical burn to the small vessels of the tympanic membrane. Further, the passage of an electrical charge produces heat as it meets with electrical resistance.[8] Therefore, heat that would be generated could not be dissipated. This explanation accounts for the singed edges seen in tympanic membrane perforations,[2,4] and for the absence of any trace of the tympanic membrane in most instances.

This explanation may also account for the tympanic membrane's remarkable regenerative characteristics in lightning injury. The tympanic membrane layers tend not to be turned in (as in our first patient's left ear), but tend to be directed centrally. This is analogous to the use of cauterizing agents on the edges of a perforation to promote spontaneous closure.[12] The remarkable regenerative power of the lightning-injured tympanic membrane is probably also due to the perforation's occurring in a healthy membrane, rather than in the scenario of chronic disease.

In summary, our 3 cases, our histologic finding, and our review of the literature clarify the mechanism of lightning injury to the ear and to the tympanic membrane in particular. Lightning strike causes a direct electrical transmission of electrical charge from an entry point through the soft tissues of the head, ears, and most important, the blood vessels. The configuration of injuries supports this mechanism. Further, the injury to the tympanic membrane itself seems to be an electrical burn that disintegrates the central tympanic membrane and leaves the edges with their unusual regenerative potency.

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MALIGNANT EXTERNAL OTITIS IN NONDIABETIC PATIENTS

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The purpose of this study is to point out that contrary to traditional belief, there is a small but significant group of nondiabetic patients with malignant external otitis. Thirty patients with a diagnosis of malignant external otitis were treated and followed up at the Department of Otolaryngology–Head and Neck Surgery, Beilinson Medical Center, between 1987 and 1991. Nine of these patients did not have clinical or laboratory evidence of diabetes. This study analyzes this group and concludes that the diagnosis of malignant external otitis should be considered by the treating physician in nondiabetic patients presenting with a *Pseudomonas aeruginosa* infection of the external ear canal. Severe pain and edematous closure of the canal, together with typical granulation tissue and failure to respond to medical treatment, are specific characteristics of this group.

KEY WORDS — high-humidity climate, malignant external otitis.

INTRODUCTION

Malignant external otitis (MEO) is a severe bacterial infection, caused by *Pseudomonas aeruginosa*, that has been described primarily in elderly diabetic patients. The process is initiated in the external auditory canal and crosses the cartilaginous-osseous junction in the inferior wall, invading the connective tissue, cartilage, bone, nerves, and blood vessels of the temporal bone and its surroundings.[1,2]

Osteomyelitis of the temporal bone, which is the most important sign of tissue invasion, can be diagnosed by a technetium 99m (Tc 99m) bone scan.[3-5]

Facial nerve palsy and involvement of cranial nerves IX, X, and XI are ominous prognostic signs, and are due to the involvement of cranial nerves at their exit from the stylomastoid and jugular foramina at the base of the skull.[1,6,7] The treatment of MEO includes thorough debridement of the ear canal, as well as topical and systemic antibiotic therapy.[8] Chandler,[1] in 1968, applied the term MEO because of its virulent, sometimes fatal course, thus emphasizing the triad of *Pseudomonas* external otitis, diabetes, and old age.[1,9,10] Although MEO has been previously described only in compromised patients, this study draws attention to a small but significant group of healthy nondiabetic patients in whom MEO may develop. Nine adult nondiabetic and otherwise noncompromised patients are described who had external otitis with granulation tissue and who did not respond to conservative treatment. We think these 9 patients represent a group that has previously not been described with MEO.

MATERIALS AND METHODS

During the years 1987 to 1991, 30 patients with a diagnosis of MEO were treated and followed up in the department of otolaryngology at the Beilinson Medical Center. The diagnosis of MEO was established according to the following criteria: 1) severe, painful inflammation of the external auditory canal manifested by granulation tissue, exudate, and edema; 2) a protracted course of at least 2 weeks, with failure of antibiotic therapy (topical and/or systemic) and/or an abnormal radionuclide bone scan (Tc 99m) of the mastoid bone; and 3) isolation of *P aeruginosa* from the exudate.

Bacteriologic culture specimens were repeatedly taken from the external ear canal of each patient included in the study. In vitro sensitivities of isolates were determined by the Kirby-Bauer method. *Pseudomonas aeruginosa* strains were considered to be sensitive to ofloxacin if the inhibition zone was at least 22 mm. All patients were treated with oral ofloxacin and local treatment, including removal of the granulation tissue and instillation of neomycin sulfate and/or gentamicin sulfate on gauze wicks. During hospitalization, blood tests were repeatedly performed (4 times daily), including fasting serum glucose values. The patients were also examined and treated twice daily, and a daily detailed follow-up report was kept.

All patients were followed up and clinically reexamined periodically for at least 6 months after discharge from the hospital. During the follow-up patients with no known history of diabetes mellitus were evaluated by the following methods.

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TABLE 1. NINE NONDIABETIC PATIENTS WITH MALIGNANT EXTERNAL OTITIS

Pt No.	Age	Sex	*Symptoms and Signs* P	D	*Otoscopic Appearance* T	Ex	GT	E	NT	A	Bone Scan	*Treatment* Drug	Days	Follow-up (mo)
1	80	F	+	−	+	+	+	+	+	−	+	Ofloxacin	14	38
2	71	F	+	+	+	+	+	+	−	+	+	Ofloxacin	24	35
												Tobramycin	12	
3	70	M	+	−	+	+	+	+	−	−	+	Ofloxacin	28	42
4	73	M	+	−	+	+	+	+	−	−	+	Ofloxacin	14	28
5	79	M	+	−	+	+	+	+	+	−	ND	Tobramycin and piperacillin	14	48
												Ofloxacin	14	
6	72	M	+	+	+	+	+	+	−	+	+	Ofloxacin	15	24
7	48	M	+	−	+	+	+	+	−	−	+	Ofloxacin	14	27
8	67	M	+	−	+	+	+	+	−	+	+	Ofloxacin	14	39
9	78	F	+	−	+	+	+	+	+	+	+	Ofloxacin	21	6

All patients had had previous antibiotic treatment for more than 2 weeks, and all patients had positive cultures for *Pseudomonas aeruginosa*.

P — pain, D — discharge, T — tenderness, Ex — exudate, GT — granulation tissue, E — edema of external ear canal, NT — necrotic tissue, A — abscess formation, ND — not done.

1. Oral glucose tolerance test, measured and interpreted according to the National Diabetes Data Group criteria.
2. Glycolated hemoglobin (GHb), quantified by affinity chromatographs (ISOLAB, Akron, Ohio; normal value range 4% to 8%).
3. Fructosamine, measured by reduction test with nitroblue tetrazolium on Hitachi System (Boehringer Mannheim GmbH; normal <285 nmol/L).

RESULTS

Clinical Features. Twenty-one patients had diabetes mellitus according to a history of oral hypoglycemic medications use and fasting blood glucose above 140 mg/dL (7.8 nmol/L) unrelated to the present infection. Nine patients, however, had no known history of diabetes mellitus. Six men and 3 women with a mean age of 71 years (range 48 to 80 years) are included in this group. All 9 patients first experienced symptoms during the summer months, and all lived on the Mediterranean coast, which has a high humidity during the summer. Otalgia, most acute at night, was the presenting symptom in all 9 patients. Complaints of discharge from the infected ear were registered by 2 of the 9. The mean duration of symptoms before diagnosis was 32 days (range 14 to 90 days). All patients had received ineffective topical and/or systemic antibiotic therapy for at least 2 weeks (Table 1). Clinical findings in all patients included tenderness of the auricle, edema of the external auditory canal, and granulation tissue. In 66% (6 of 9) necrotic tissue and/or abscess formation was found (Table 1).

Bone Scanning. An abnormal Tc 99m scan was obtained in 8 patients. One patient did not have a Tc 99m scan, but the patient was judged to have MEO on the criteria of extreme pain, presence of granulation tissue, and failure of prior local and systemic therapy of more than 2 weeks' duration.

Bacteriology. Pseudomonas aeruginosa sensitive to ofloxacin was isolated several times from the external auditory canal of all patients.

Treatment. The main mode of treatment was cleansing of the external canal and debridement of granulation tissue. All patients were treated with ofloxacin (200 mg twice daily), which was given for 14 to 28 days. Two patients received in addition parenteral antibiotics (piperacillin sodium 200 to 300 mg/kg per day and/or tobramycin sulfate 4.5 mg/kg per day). The mean duration of drug therapy was 19.1 days (Table 1).

Follow-up. Subjective improvement had occurred in all our patients 5 days after surgical removal of granulation tissue and treatment with ofloxacin, and objective improvement occurred in all patients after 7 to 12 days of treatment. All patients were followed up and clinically reexamined periodically for a mean period of 32 months (range 6 to 48 months; Table 1). In order to eliminate overt diabetes mellitus, all patients with no prior history of diabetes were evaluated by an oral glucose tolerance test and determination of GHb and fructosamine levels at least 6 months after a complete recovery. Two patients had impaired glucose tolerance (22%, 95% confidence interval 1% to 45%), and 7 patients had normal glucose tolerance. All GHb and fructosamine levels were within the normal range (Table 2).

DISCUSSION

The precise pathogenesis of MEO is unknown.

TABLE 2. DIABETIC STATUS

Pt No.	Fasting Blood Glucose (mg/dL)	Oral Glucose Tolerance Test	Glycolated Hemoglobin (%)	Fructosamine (nmol/L)
1	77	Normal	6.7	225
2	83	Normal	5.5	260
3	98	Impaired	5.8	280
4	93	Normal	6.2	240
5	97	Normal	5.8	225
6	107	Normal	5.6	230
7	83	Normal	5.9	225
8	95	Impaired	5.4	245
9	77	Normal	6.0	255

Aging and diabetes mellitus are both associated with altered immune function. The specific defects, however, are unclear. Histopathologic studies of the capillaries in the skin and subcutaneous tissue overlying the temporal bone have confirmed a thickening of periodic acid–Schiff–positive material in the subendothelial basement membrane. It is possible that accelerated small vessel disease related to age but not to diabetes may explain the MEO in the nondiabetic group described here.[2,11]

Postulations of the presence of MEO in nondiabetics have been made by Babiatzki and Sade[8] and supported by Rubin and Yu.[2]

Between 1987 and 1991, 30% of our 30 patients with a diagnosis of MEO treated in our department were nondiabetic. There was no history of ear disease or any underlying illness except for ischemic heart disease and hypertension in 3 patients. There was no history of ear irrigation with water 3 weeks before the onset of symptoms. All patients except 1 belonged to the elderly age group (mean age 71 years), making it impossible to exclude some degree of peripheral vascular disease. The prevalence of impaired glucose tolerance in this group was the same as that of the general population.[12,13]

Malignant external otitis rarely occurs in healthy, nondiabetic, nonimmunocompromised patients.[2,8,11,14-18] Although MEO is traditionally connected with diabetes mellitus, this study illustrates that it is not confined to the diabetic patient. Many of our patients with MEO had no evidence of clinical or chemical diabetes. We believe that the diagnosis of MEO should be considered in any patient presenting with *P aeruginosa* infection of the external auditory meatus with otalgia, edema, and granulation tissue in the external ear canal if the bone scan findings are abnormal and/or if there is failure to respond to antibiotic therapy within 2 weeks.

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SUDDEN SENSORINEURAL HEARING LOSS ASSOCIATED WITH SLOW BLOOD FLOW OF THE VERTEBROBASILAR SYSTEM

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To determine the characteristics of sudden deafness associated with slow blood flow (SBF) within the vertebrobasilar arteries, we evaluated 57 patients with sudden deafness using magnetic resonance imaging (MRI). We detected SBF in 12 (21%) patients, predominantly men over 50 years of age. A second MRI performed in 5 patients 2 months after the onset of symptoms showed recovery of blood flow. All 12 patients complained of vertigo. Audiological and neurotologic tests suggested that hearing loss mainly involved the inner ear. Our findings suggest that unless central lesions are detected, headache, hypoesthesia of the external ear canal, and electronystagmographic abnormalities are signs of SBF. Because sudden deafness may recur in patients who have SBF, they should be monitored and treated to prevent recurrence.

KEY WORDS — etiology, magnetic resonance imaging, sudden sensorineural hearing loss, vertebrobasilar insufficiency.

INTRODUCTION

Sudden sensorineural hearing loss, so-called sudden deafness, is an abrupt loss of hearing that occurs instantaneously or is present on awakening; hearing impairment occurs within a few hours of initial symptoms.[1-4] Patients may or may not experience tinnitus, vertigo, nausea, and/or vomiting. Hearing loss recurs in up to 50% of cases over time.[4]

It is certain that there is no single cause of sudden deafness; the symptom of decreased hearing is the final outcome for many potential insults to the inner ear. The 3 most commonly accepted causes are viral infections, circulatory disorders, and labyrinthine membrane rupture.[1,3,5,6] Increases in specific antibody titers found in some patients with sudden deafness suggest a viral cause.[4,7] Labyrinthine membrane rupture has been observed in some patients during tympanotomy. Although histopathologic evidence of circulatory disorders has been identified in human temporal bones,[8,9] clinically, circulatory disorders are difficult to diagnose. Fisch et al[10] found significantly lower perilymphatic oxygen tension in patients with sudden deafness, but it was impossible to determine whether this finding represented a primary or a secondary effect.

Although severe unilateral hearing loss has occurred in patients with basilar artery occlusion or vertebrobasilar insufficiency,[9,11,12] sudden deafness was rarely diagnosed in these patients because of the presence of other neurologic deficits. However, we recently obtained magnetic resonance imaging (MRI) evidence that peripheral vestibular disorders in elderly patients were frequently associated with brain stem lacunae and/or slow blood flow (SBF) of the vertebrobasilar system[13,14]; some of these patients had been classified before MRI as having sudden deafness because they experienced an abrupt hearing loss unaccompanied by other neurologic deficits.

The labyrinthine artery (LA) may arise from the basilar artery (BA), the anterior inferior cerebellar artery (AICA), or occasionally the posterior inferior cerebellar artery with a rostral vertebral artery (VA) or caudal BA origin. The AICA may arise on either side of the BA, anywhere from the level of the caudal part to the middle of the pons.[15] Because of the variable origin of the LA, involvement of either the BA or the rostral VA can lead to decreased blood flow in the LA.

We evaluated 57 patients with sudden deafness using MRI to determine the characteristics of sudden deafness associated with decreased blood flow within the BA and the rostral VA.

SUBJECTS AND METHODS

Subjects. We evaluated 57 patients (31 male, 26 female; age range 12 to 76 years; mean age 52 years),

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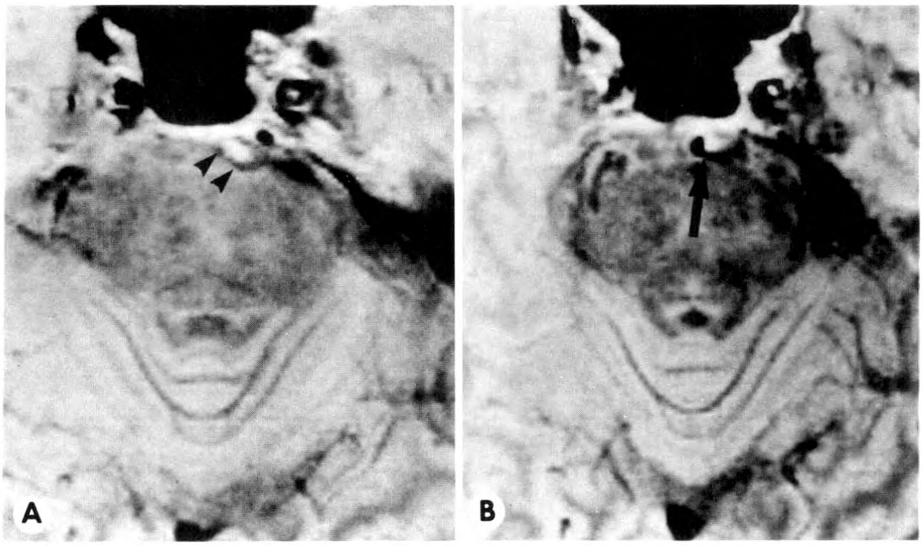

Fig 1. (Patient 4) Proton-density magnetic resonance images. A) At onset of sudden deafness, high-intensity signal indicating slow blood flow is observed in caudal basilar artery (arrowheads). B) Marked decrease in signal intensity is observed in caudal basilar artery (arrow) 2 months after onset of symptoms, indicating recovery of blood flow.

who came to the Department of Otolaryngology at Kameda General Hospital between January 1991 and November 1992 complaining of sudden deafness. Patients whose deafness was related to a definite cause, such as Meniere's disease, acoustic neurinoma, or large infarcts of the hindbrain, were excluded from the study.

Magnetic Resonance Imaging. A superconducting 1.5-T magnetic resonance system was used with a slice thickness of 4 mm. Proton-density images (TR/TE 3,000/15) and T2-weighted images (TR/TE 3,000/90) were obtained in both the axial and coronal planes. Slow blood flow within the BA or the rostral VA was identified as an area with high-intensity signal on proton-density images.[13,14,16] Lacunar infarcts appeared as small spots with high-intensity signal on T2-weighted images.[13]

Evaluation of Patients With Slow Blood Flow. Patients in whom SBF was detected underwent physical, neurotologic, neurologic, and neurophysiologic examinations. Antibody titers of several viruses such as mumps virus, adenovirus, and herpesvirus were measured, and speech and pure tone audiometry examinations were performed. Fowler's alternate binaural loudness balance test, Bekesy's audiometry, and auditory brain stem response (ABR) testing were performed in 8 patients who did not show profound hearing loss. Neurotologic tests, including electronystagmography, were performed to assess pathologic nystagmus (changes of fixation, gaze, and head position), vestibulo-ocular reflex function (caloric testing), and visual-ocular control (saccade and smooth pursuit). The caloric test result was evaluated in terms of the maximal velocity of slow phase of the nystagmus evoked by stimulation with 10 mL of ice water: severe impairment, maximal velocity of slow phase <1°/s; moderate, ≥1°/s to <10°/s; slight, ≥10°/s to <20°/s; and normal, ≥20°/s.

The patients received conventional treatment with steroids and vasodilators. In 5 patients, a second MRI scan was performed 2 months after onset of symptoms. Informed consent to testing was obtained for all patients.

RESULTS

Slow blood flow (Fig 1A) was found in 12 (21%) of 57 patients, predominantly men over 50 years of age (Table 1), representing 36% of the 33 patients 50 years of age or older. Four of the 12 patients also showed a lacunar infarct in the central portion of the ventral pons (Fig 2). Five patients had been receiving treatment for hypertension. No symptoms of upper respiratory tract infection or increases in antibody titers were observed. All 12 patients complained of vertigo, with headache being the second most common complaint. In 4 patients, sudden deafness recurred in the same ear 4 months to 2 years after the first episode. In 1 patient (patient 8), a large infarct related to occlusion of the AICA, which resulted in total deafness, facial palsy, dysarthria, and ataxia, was eventually identified. A fifth patient (patient 9) experienced an episode of sudden deafness in the opposite ear 1 year after the initial episode.

Hearing levels at the initial examination varied from 30 dB to total loss (scale out; Table 2). Pure tone audiograms showed predominantly flat loss, high-tone loss, or total loss. Recruitment phenomena were present in all patients examined, while the ABR showed normal interpeak latencies. Of a total of 17 episodes in 12 patients, hearing recovered to within 20 dB in 4 episodes. Hearing gradually worsened in 2 episodes. In patients who experienced recurrence, hearing was more severely impaired after the second

TABLE 1. CHARACTERISTICS OF PATIENTS WITH SUDDEN DEAFNESS ASSOCIATED WITH SLOW BLOOD FLOW

Pt	*Age*	*Sex*	*Symptoms Other Than Hearing Loss*
1	51	M	Vertigo, headache
2	54	M	Vertigo
3	59	M	Vertigo, vomiting, headache
4	59	M	Vertigo
5	61	M	Vertigo, headache
6	62	M	Vertigo, vomiting, headache
7	62	F	Vertigo
8	65	M	Vertigo, vomiting, incoordination
9	67	M	Vertigo, vomiting, headache
10	68	M	Vertigo, headache
11	68	M	Vertigo, vomiting
12	70	F	Vertigo

episode.

Five patients noted hypoesthesia in the external canal of the involved ear. Horner's sign was not present in any patient. Gaze nystagmus was directed toward the involved side on the first few days after onset, but then changed to the contralateral side. On caloric tests, patients commonly showed moderately to severely decreased responses in the involved ears. Abnormalities related to smooth pursuit and saccade were found in 2 patients, who also had brain stem lacunae.

In 5 patients who underwent a second MRI scan 2 months after onset of symptoms, decreased signal intensity was observed within the BA and rostral VA on T1-weighted images, indicating recovery of blood flow in these arteries (Fig 1B).

DISCUSSION

Decreased blood flow in the LA may be related to decreased blood flow within the vertebrobasilar system, or to occlusion or vasospasm of the LA itself. Although the occlusion and vasospasm are impossible to detect, decreased vertebrobasilar flow can be demonstrated with MRI. Slow blood flow was detected in 12 (21%) of 57 patients with sudden deafness, which represented 36% of the 33 patients 50 years of age or older.

The significance of SBF in sudden deafness is unknown. We previously reported that SBF was absent in healthy young subjects and was found in only 6 (11%) of 57 patients 50 years of age or older, who underwent MRI for evaluation of symptoms such as headache[14]; the incidence of SBF is significantly higher ($p < .01$) in elderly patients with sudden deafness. Further, subsequent MRI scans performed in 5 patients showed recovery of blood flow in the vertebrobasilar system, indicating a temporary decrease in blood flow at the onset of sudden deafness. In 1 patient, the AICA eventually occluded. These findings suggest a possible correlation between SBF and sudden deafness.

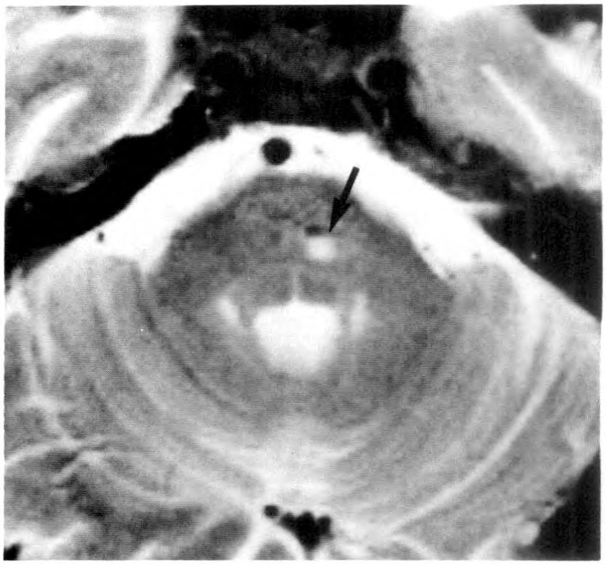

Fig 2. (Patient 3) T2-weighted magnetic resonance image. High-intensity signal spot indicating lacunar infarct is present in central portion of left ventral pons (arrow).

The patients with SBF were predominantly men, and all were over 50 years of age. Five had been treated for hypertension. That these patients were older than average for patients with sudden deafness[1,2] suggests that SBF may contribute to sudden deafness, especially in elderly patients at high risk for atherosclerosis.

Recruitment phenomena were found in all examined patients without profoundly impaired hearing; none of these patients showed prolongation of interpeak latencies on the ABR. Canal paresis was present in almost all patients; only 2 patients, who also had brain stem lacunae, exhibited central vestibular abnormalities. These observations suggest that hearing loss mainly involved the inner ear, especially in patients with mild to moderate hearing loss. In the patients with profound to total hearing impairment, the possibility remains that the central auditory pathway, including the cochlear nerve, may also be affected.

A human temporal bone study performed by Gussen[8] also suggests that the inner ear may be more vulnerable to ischemia within the vertebrobasilar system than the cochlear and vestibular nerves. She examined a patient with sudden deafness accompanied by dizziness, who had also had hypertension and rheumatoid arthritis. This patient died of bronchopneumonia 2 months after the onset of symptoms. Autopsy findings included subarachnoid hemorrhage, total loss of the organ of Corti, severe degenerative

TABLE 2. HEARING LOSS, RECOVERY, SPEECH DISCRIMINATION AFTER RECOVERY, AND CALORIC TEST RESULTS

Pt	*Ear**	*Type of Hearing Loss*	*Initial PTA (dB)*	*Recovery PTA (dB)*	*Speech Discrim (%)*	*Canal Paresis*
1	L	Dip	95	70	30	Moderate
2	R	Flat	65	85	25	Severe
3	R	High-tone	60	15	95	Moderate
4	R	Flat	100	70	35	Moderate
5	L	High-tone	40	100	NE	Severe
6	L	Flat	55	40	80	Moderate
	L	ND	ND	ND	NE	Severe
7	R	Dip	45	15	100	Moderate
8	L	Low-tone	30	15	100	None
	L	ND	ND	ND	NE	Severe
9	L	ND	ND	ND	NE	Severe
	R	Flat	105	70	45	Severe
10	R	Flat	70	45	65	Moderate
	R	High-tone	65	65	40	Moderate
11	R	Flat	50	20	95	Slight
	R	Flat	60	60	50	Moderate
12	L	Flat	85	60	50	Moderate

PTA — average hearing level on pure tone audiometry, ND — not detectable, NE — not examined.

*Patients 6, 8, 10, and 11 experienced 2 episodes in same ear.

changes of the distal cochlear nerve fibers, and loss of macula and nerve fibers of the sacculus. There was only a slight decrease in the number of fibers in the cochlear and vestibular nerves within the internal auditory canal. On the other hand, Kitamura and Berreby[9] found in a patient who died of pontine infarction that occlusion of the VA and BA resulted in severe degenerative changes, not only in the membranous labyrinth, but also in the cochlear and vestibular nerves.

Transient or developing pathologic changes in the ABR have been observed during surgical occlusion of the BA[17] and thrombotic occlusion of the BA[18] in patients who showed severe neurologic deficits. No severe neurologic abnormalities were observed in our patients. A pathologic ABR is rarely seen in patients with small midline pontine infarcts, while patients with Horner's sign commonly show an abnormal ABR because of the proximity of the sympathetic tracts and the auditory pathways.[19] Horner's sign was not present in our patients. When lacunae were present, they were found in the central portion of the ventral pons, far from the auditory pathways. These findings may explain the normal ABRs in our patients.

Vertigo was the characteristic complaint in our patients. Six patients also noted headache, which is frequently found in patients with vertebrobasilar insufficiency.[12] Neurotologic examinations revealed hypoesthesia of the external ear canal, which is sometimes found in patients with tumors of the cerebellopontine angle, in 5 patients. Abnormalities in smooth pursuit and saccade, which indicate a central vestibular disorder, were found in 2 patients. Unless central lesions are detected, these symptoms and signs appear to suggest the presence of SBF.

Patients with sudden deafness associated with SBF may experience recurrences. Hearing loss may worsen after the second episode. Thus, these patients should be followed up and treated to prevent recurrence.

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IMPROVEMENTS IN RESPIRATORY AND PSYCHOSOCIAL FUNCTIONING FOLLOWING TOTAL LARYNGECTOMY BY THE USE OF A HEAT AND MOISTURE EXCHANGER

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A prospective clinical study in 61 patients was undertaken to investigate the subjective and objective influence of a heat and moisture exchanger (HME) on the respiratory and psychosocial problems following total laryngectomy. Although statistical comparisons failed to detect significant differences between the experimental and the control groups, there was a clear trend toward improvements in respiratory and psychosocial functioning in the experimental group. Analyses of differences over time within the HME user group showed significant reductions in the incidence of coughing, the mean daily frequency of sputum production, forced expectoration, and stoma cleaning. Significant improvements were also found in shortness of breath, fatigue and malaise, sleep problems, levels of anxiety and depression, and perceived voice quality. Pulmonary function tests showed significant improvements in inspiratory flow and volume values following use of the HME. This objective improvement in inspiratory pulmonary function reflects the decrease in sputum production reported by the patients.

KEY WORDS — heat and moisture exchanger, laryngectomy, pulmonary function, quality of life, voice restoration.

INTRODUCTION

After total laryngectomy, patients frequently experience a range of respiratory problems, including excessive sputum production, coughing, forced expectoration to clear the airway, and stoma cleaning.[1] These problems can have a serious impact on many aspects of daily life, including increased fatigue and sleeping problems, compromised voice quality, disrupted social contacts, and heightened psychologic distress.[1]

The most likely cause of the respiratory problems after total laryngectomy is the disconnection between the upper and lower airways, that is, the loss of the nose's cleaning, heating, and moisturizing effects on inhaled air. Air inhaled after laryngectomy is not conditioned, and this can result in irritation of the bronchial mucosa, coughing, increased sputum production, and crusting.[2] Moreover, the pulmonary physiology may be negatively influenced by the decrease in airway resistance of the stoma. Although respiratory problems tend to diminish somewhat in the first year after surgery, almost all patients continue to suffer from these symptoms. Frequently, there is an increase in respiratory symptoms during the winter.[3]

In an attempt to restore some of the lost "nose" functions, we previously investigated the influence of a heat and moisture exchanger (HME) on respiratory symptoms after total laryngectomy.[4] Use of a similar device has been demonstrated to reduce the diurnal loss of water through the exhaled air by approximately 60% (250 to 300 mL).[5] The filter also increases airway resistance. Moreover, the results of this study indicated that an HME can significantly reduce many respiratory symptoms after total laryngectomy, including the frequency of daily sputum production and the incidence of stoma cleaning, even after a relatively short period of use (6 weeks).[4] Symptoms of fatigue and malaise were reduced and social contacts improved significantly over time as well. However, the combination of a voice prosthesis and this HME created some difficulties. Some patients had difficulty creating an airtight seal around the stoma in order to speak properly. One of the factors contributing to this problem might be the relatively high resistance of the voice prosthesis then employed.[6] Other contributing factors were the rigidity of the HME and the difficulty of fixation, in case of a deep or asymmetrically situated stoma.

Although the results of this earlier study were encouraging, the absence of an appropriate control group, the relatively short follow-up period, and the absence of objective measures of lung function sug-

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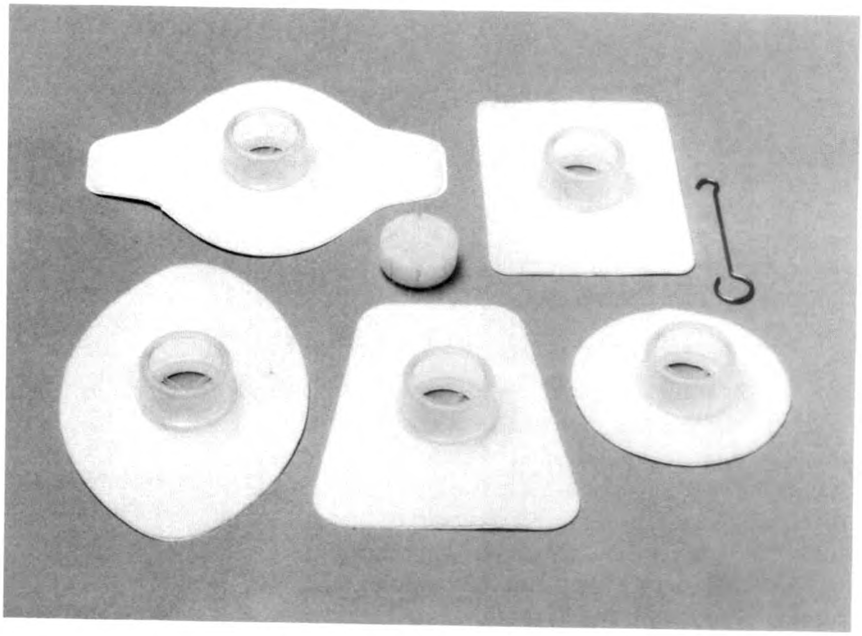

Freevent heat and moisture exchanger: 5 different shapes of base-holder, cassette containing heat and moisture exchanging filter, and hook used by patient to remove filter cassette.

gested the need for further research. Moreover, certain technical advances achieved since the first study held promise for resolving the problems observed in using an HME. First, a new voice prosthesis (Provox), developed in our institution, became available.[7] Its low airflow resistance could make the occlusion of the stoma to obtain speech less critical. Second, a new type of HME (Freevent, Pharma Systems, Söderham, Sweden) became available that is more flexible and comes in various shapes, thus facilitating tailoring to the anatomic characteristics of individual patients.

The current clinical study was undertaken to 1) investigate the influence of this new type of HME on physical and psychosocial consequences of total laryngectomy, 2) determine if subjective improvements in pulmonary function could be confirmed with objective lung function measures, 3) determine whether the new HME could successfully resolve the problems concerning fixation, and 4) investigate whether the combination of the new HME and voice prosthesis could resolve the previously observed speech problems.

PATIENTS AND METHODS

All laryngectomized patients without prior experience with an HME who visited The Netherlands Cancer Institute outpatient clinic during the 4-month winter period of 1990-1991 were requested to participate in the study. Two elderly patients refused to participate. The 48 patients who gave their consent were randomized either to the experimental group to test the HME ($n = 24$), or to a no-treatment control group ($n = 24$). An additional group comprising 15 patients who participated in our earlier HME study[4] was included in order to compare their experience with the previous device and the new device. The majority of patients (89%) were men. The mean age of the sample was 66 years (range 46 to 84). The time since total laryngectomy varied from 3 months to 24 years, with a median of 2.8 years.

The patients randomized to the HME group and the group from our previous study were provided with HMEs for a 3-month period. The HME (Freevent) used in this study consists of a silicone housing (with a diameter of 22 mm) placed in adhesive tape and a removable filter consisting of a nonwoven, monofilament polymer (polypropylene and polyethylene). This device is glued to the skin around the stoma as well. When the filter becomes obstructed with secretions, it is not necessary to replace the complete device, but only the filter. The tape is available in 5 different shapes (see Figure). The best possible fitting plaster was prescribed for each patient. Patients were instructed how to fix the device to the skin around the stoma and how to replace the filter when it became obstructed with secretions. The patients were instructed to use the HME, if possible, both day and night.

All patients were interviewed by the same investigator (A.H.A.) at the start of the study and again after 3 months during a routine follow-up visit to the outpatient clinic. Both interviews required, on average, 1 hour to complete.

The content of the interview has been described in detail elsewhere.[1] Briefly, the first interview evaluated the presence and severity of respiratory symptoms (cough, sputum production, shortness of breath, wheezing, bronchial asthma, nasal discharge, pulmonary infections, and forced expectoration), fatigue

TABLE 1. WEEKLY INCIDENCE OF COUGHING BEFORE AND AFTER 3-MONTH STUDY PERIOD

	*HME Group (N = 37)**		*Control Group (N = 24)*	
Days per Week	*Before*	*After*	*Before*	*After*
0	12	20	12	11
1 or 2	2	—	1	—
3 or 4	2	—	1	1
5 or more	21	17	10	12

HME — heat and moisture exchanger.

*p < .05.

TABLE 2. MEAN DAILY FREQUENCY OF RESPIRATORY SYMPTOMS BEFORE AND AFTER 3-MONTH STUDY PERIOD

	HME Group (N = 37)		*Control Group (N = 24)*	
Symptoms	*Before*	*After*	*Before*	*After*
Coughing	9.5	7.2	7.4	8.3
Sputum production	10.4	7.2*	11.6	9.9
Forced expectoration	10.2	6.9*	11.7	9.8
Stoma cleaning	4.7	3.2†	5.1	5.0

HME — heat and moisture exchanger.

*p < .005.

†p < .01.

and sleep problems, perceived adequacy of voice rehabilitation, social contacts, and anxiety and depression. The second interview included additional items on various practical aspects of the device, such as the number of filters and plasters used per day (patients were asked to report the number of HMEs they used during the first and last weeks of the 3-month trial period), use during the night, skin irritation, problems with adhesion to the skin, fixation during coughing, problems with replacing the filter, and airway resistance. Finally, patients were asked to provide an overall rating of the usefulness of the HME and to report whether they intended to use it in the future and whether they would recommend its use to fellow patients.

Pulmonary function tests were performed on all patients on entering the study and 3 months thereafter, and included maximum vital capacity (VC Max), total lung capacity, forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), maximum expiratory flow volume at 50% (MEF_{50}), and the same measurements for inspiratory flow or volume (FIV_1, PIF, and MIF_{50}, respectively).

The base-holder (the silicone housing placed in adhesive tape) of the HME was used to connect the patient to the standard lung function testing equipment (standard Masterlab Transfer, Erich Jaeger GmbH, Würzburg, Germany). The test results obtained in this way provide a more valid representation of the actual lung function of the laryngectomized patient than do the results obtained with the conventional cuffed tracheal cannula.[8]

Statistical comparisons between the experimental and control groups were made by means of a repeated measures multivariate analysis of variance and the Mann-Whitney U test. Differences over time within groups were tested with paired Student's *t* tests and the Wilcoxon nonparametric tests for paired observations. A 2-tailed p value below .05 was considered significant.

RESULTS

Group Differences and Changes Over Time. Statistical comparisons failed to detect any significant differences between the experimental and the control groups in respiratory and other physical symptoms, voice rehabilitation, or psychologic and social functioning. In part, the failure to detect statistically significant group differences can be attributed to the small sample size and the resulting restriction in statistical power. Nevertheless, the results suggested a trend toward diminished respiratory problems, a reduction in levels of fatigue and malaise, improved lung function, and improved voice quality among the HME user group. Additional analyses were carried out to examine differences over time within the group of HME users (the experimental group and the 15 experienced patients, combined) and within the control group. These within-group analyses do not require as large a sample size as do the between-group multivariate analyses.

Of the 24 patients randomized to the HME group, 1 patient died during the observation period of intercurrent disease, and another patient suffered from severe, prolonged bronchitis that prevented him from using the HME. Combined with the 15 experienced patients, this resulted in a group of 37 patients that used the HME. Of these 37 patients, 19 (51%) used the HME continuously, 7 (19%) used the device frequently but irregularly, and 11 (30%) discontinued use after 3 to 42 days. The mean number of filters employed by those patients who used the HME continuously decreased significantly, from 20.9 to 16.4 filters per week (p < .05). The mean number of base-holders used did not change significantly over time (from 10.2 to 8.6 base-holders per week).

The number of patients who did not cough at all increased from 12 to 20 patients (Table 1), and the mean daily frequency of sputum production, forced expectoration, and stoma cleaning decreased significantly among the HME users (Table 2). Significant improvements were also observed within the HME group over time in shortness of breath (p < .01), feelings of fatigue and malaise (p < .01), sleep problems (p < .01), symptoms of anxiety and depression

TABLE 3. SEVERITY OF PROBLEMS AFTER USING HME (N = 37)

	Frequency (%)			
	None	*Slight*	*Moderate*	*Great*
Removal painful	69	25	6	0
Skin irritation	64	25	8	3
Loosening by coughing	47	20	22	11
Inadequate adhesion	81	8	8	3
Replacement filter	97	3	0	0

HME — heat and moisture exchanger.

($p < .01$), and perceived voice quality ($p < .001$).

Within the control group ($n = 24$) a slight, statistically nonsignificant decrease in the mean frequency of sputum production and forced expectoration was noted. A significant reduction in sleep problems ($p < .05$) and symptoms of anxiety and depression ($p < .05$) was also found. In part, these observed changes in the control group can be attributed to those patients ($n = 7$) for whom the time since surgery was less than 1 year. That is, during the first postoperative year, respiratory problems tend to diminish spontaneously. With the exclusion of these 7 patients, the decrease in sleeping problems and levels of anxiety and depression was no longer statistically significant. In the HME group there were also 5 patients who had been laryngectomized less than a year earlier. When these 5 patients were excluded, the improvements in the HME group remained statistically significant.

HME Users' Experience. Increase in airway resistance due to the filter was never given as a reason for discontinuing the use of the HME. Only a few patients ($n = 5$) reported that they sometimes removed the filter during the first days of the study period.

Half of the patients with a voice prosthesis (16 of 31) reported problems with the occlusion of the HME in order to speak. Interestingly, a few patients ($n = 3$) mentioned that the HME facilitated speaking, while their intelligibility also improved. Other problems relating to the use of the HME are shown in Table 3. The removal of the plaster was seldom painful, and replacement of the filter did not present any problems. A few patients ($n = 3$) were troubled by skin irritation. One third of the patients complained about loosening of the plaster by coughing, although in general, patients were satisfied with the adhesive properties of the plaster.

After 3 months of HME use, 61% of the patients reported that their respiratory symptoms had diminished, with the remaining 39% experiencing no significant benefit. Fifty-eight percent of the patients stated that they intended to continue using the HME. All patients reported that they would recommend that fellow patients try the HME, with 25% stating that they would strongly recommend its use. Fourteen of the 15 patients who participated in the previous HME study expressed a preference for the Freevent HME over the Stom-Vent HME. The main reasons for this preference were that it facilitated speech ($n = 4$) and had better adhesive properties ($n = 5$).

TABLE 4. PULMONARY FUNCTION BEFORE AND AFTER 3-MONTH STUDY PERIOD (N = 30)

	Before	*After*
VC Max	3.5	3.6
FEV$_1$	2.3	2.4
PEF	6.1	6.5
MEF$_{50}$	2.1	2.4
FIV$_1$	2.9	3.1*
PIF	4.2	5.0†
MIF$_{50}$	3.7	4.6†

See text for abbreviations.

*$p < .05$.

†$p < .005$.

Pulmonary Functioning. Pulmonary function tests were available for 30 of the 37 HME users. In 2 cases, 1 of the 2 pulmonary function tests was not available. In 5 cases the test results could not be used, because the first lung function test had been performed with a tracheal cannula instead of the HME base-holder. Earlier research has demonstrated that these 2 methods produce significantly different test results.[8]

The results of the pulmonary function tests indicated that the HME was more effective on the inspiratory flow and volume than on the expiratory flow and volume. Within the HME group, a significant improvement over time was found in the FIV$_1$ ($p < .05$) and in the MIF$_{50}$ and PIF ($p < .005$; Table 4). No such improvements in pulmonary functioning were found for the control group.

DISCUSSION

The principal aim of this prospective clinical study was to determine whether the use of an HME diminishes respiratory symptoms in laryngectomized patients and thereby improves the quality of their lives, and to determine if subjective improvements in pulmonary function could be confirmed by pulmonary function tests. In this study a new type of HME was tested whose design was intended to resolve previously observed problems associated with the combined use of an HME and a voice prosthesis and with fixation problems due to a deep and/or asymmetrically positioned stoma.

Given the fact that approximately half of all laryngectomized patients report an increase in respiratory problems during the winter season,[1,3] all patients needed to be interviewed and subjected to pulmonary tests during the same season. The restricted period of patient accrual resulted in a relatively small sample size, thus limiting the power of the current study to detect significant differences between the experimental and control groups. However, among the HME users group a clear trend was noted toward diminished respiratory problems and fatigue, and toward improved pulmonary function and voice quality.

Additional analyses of within-group changes over time confirmed that for the HME user group, there was a significant reduction in respiratory problems and in the need to clean the stoma over the 3-month study period. As a consequence, among the HME users a positive change was noted over time in several aspects of daily life, including decreased fatigue and sleep problems, decreased psychologic distress, and improved voice quality. These findings are, in general, in accordance with our previous HME study, in which a significant reduction was observed in sputum production, stoma cleaning, and fatigue, and a significant improvement was noted in social contacts.[4]

Half of the patients using a voice prosthesis continued to have difficulties with the occlusion of the stoma in order to speak. For some patients the diameter of the HME filter (22 mm) was too large for it to be easily rendered airtight with a finger. The use of a special adapter ring (with a smaller diameter) can minimize this problem.

A proper fitting and fixation of the HME for irregular or deep and/or asymmetrically situated stomas was possible, given the availability of 5 different HME plaster shapes. The anatomically shaped plaster was particularly effective in this regard. The adhesive properties of the HME used in the current study were better than those of the earlier model. An important practical advantage of the Freevent HME is that the plaster does not need to be removed when replacing a filter obstructed by secretions. However, some experience and skill is required to clean the stoma while the base-holder is still glued over the stoma. The patient may require some assistance (for example, from a spouse) in performing this task. As was noted in our previous study, irritation caused by an allergic skin reaction to the HME led a few patients (n = 3) to discontinue use of the device. Loosening by coughing diminished with the drop in sputum production. Some patients also mentioned that transpiration sometimes resulted in loosening of the plaster. Cleaning the skin with alcohol contributes to the resolution of this problem. Patients who had experience with the previous HME preferred the current model, mainly because of the improved adhesive properties. While patients also reported that it was easier to speak with the Freevent HME, this is most likely the result of the lower resistance of the Provox voice prosthesis used in this study.

The results of the pulmonary function tests indicated improved function over time, particularly in inspiratory flow and volume values. This objective improvement in inspiratory pulmonary function reflects the decrease in sputum production reported by the patients. These objective and subjective results are indicative of a recovery of the upper airway mucosa. This improved lung function is all the more noteworthy given the relatively short period of HME use (only 3 months). Other lung function values such as the VC Max and the total lung capacity did not change significantly over time. As the median time elapsed since surgery was 2.8 years, it is probable that continuous exposure of the bronchial mucosa to "unmodified" air resulted in increased irritation, coughing, excess sputum production, and crusting. It is not likely that these problems can be resolved completely in 3 months' time. Further improvement in pulmonary function might be expected with the prolonged use of the HME. Additional support for the beneficial effect of an HME on pulmonary function has recently been reported in a study of patients with exercise-induced asthma.[9] The use of a mask containing an HME was found to be as effective as conventional medication in the prevention of this form of obstructive lung disease. This suggests that besides water loss, heat loss (both are thought to be the main causes of this form of asthma[10]) plays a causative role in the pulmonary problems of laryngectomized patients.

In conclusion, both the objective and subjective results of this prospective study suggest that the use of an HME can effectively reduce the physical and psychosocial problems following total laryngectomy. Because of the small sample size, it is not possible to attribute all of the observed improvements to the use of an HME. Nevertheless, the results of the within-group analyses of change over time fully support the results of our previous study concerning the positive effect of an HME. The pulmonary function tests, indicating an increase in the inspiratory flow and volume values for HME users, support the beneficial effect of the HME on upper airway mucosa recovery.

It should be emphasized that the HME is a medical device. Counseling by a physician is needed to ensure proper use of the device and to obtain optimal results. Further research is in progress to investigate whether use of an HME immediately following total laryngectomy can prevent the development of respiratory symptoms.

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CURRENT TRENDS, CONTROVERSIES, AND PERSPECTIVES IN RHINOLOGY AND SINUS SURGERY

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Ann Otol Rhinol Laryngol 102:1993

LOCALIZED AMYLOIDOSIS OF THE LARYNX: EVIDENCE FOR LIGHT CHAIN COMPOSITION

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We report the biochemical characterization of amyloid fibrils from a patient with localized amyloidosis of the epiglottis and larynx. Biopsy specimens showed amorphous material consistent with amyloid deposits with a plasmacytic infiltrate. Both plasma cells and amyloid deposits stained positively by immunohistochemistry for κ light chains. Amyloid fibrils were isolated. The major constituent resolved as a 13 kd band was sequenced and found to be consistent with a κ1 light chain. A tryptic digest was carried out and 3 tryptic peptides were sequenced defining the first 45 residues of the protein and residues 110 through 119. Four amino acid substitutions were found, 3 of which have not been described previously. This study defines the immunoglobulin origin of amyloid deposits in localized amyloidosis. The benign nature of localized amyloidosis suggests that a localized clone of plasma cells producing an amyloidogenic light chain may represent the pathogenetic mechanism of this disease, which appears to be a form of plasma cell dyscrasia.

KEY WORDS — amyloidosis, immunoglobulin, immunohistochemistry, kappa light chain, larynx, plasma cell dyscrasia, protein sequence.

INTRODUCTION

Localized amyloidosis is an uncommon disorder of unknown cause that occurs in the absence of systemic amyloidosis or associated disease. Sites of involvement include, but are not limited to, the head and neck, aerodigestive tract, lower respiratory tract,[1-4] urinary bladder,[5] and skin.[6] We report the immunohistochemical characterization and protein sequence of the amyloid protein from a case of localized amyloidosis of the epiglottis and larynx.

There is much evidence to suggest that the amyloid protein in localized amyloidosis of the respiratory tract is of immunoglobulin origin. In numerous cases, localized amyloid deposits have been found in association with plasma cell infiltrates that may be the source of the amyloid protein.[2,3,7-10] In some cases of diffuse pulmonary amyloidosis without systemic amyloidosis, a serum monoclonal gammopathy composed of either κ or λ light chains has been found.[11,12] Immunohistochemical studies of localized amyloid tissues have helped define the nature of these deposits. Mufarrij et al[2] describe a case of nasal amyloid in which both localized amyloid deposits and adjacent tissue plasma cells stained positively for λ light chains. Laden et al[3] found that a specimen of nodular pulmonary localized amyloid stained positively for both κ and λ light chains in both localized amyloid deposits and the adjacent plasma cells, implying a polyclonal origin. In contrast, Lewis et al[13] found that in a series of 22 consecutive cases of localized laryngeal amyloid, 12 amyloid specimens stained positively for only λ light chains and 5 stained positively for only κ light chains. In 12 cases, plasma cells found in the interstitium stained positively for both κ and λ light chains. In 2 studies, the amyloid fibrils in localized amyloid have been isolated and characterized. Page et al[10] found that amyloid protein from a nodular pulmonary lesion contained a λ light chain as determined by cross-reactivity with anti-λ Bence-Jones protein immune serum by double immunodiffusion and peptide map pattern. In a more recent study, Westermark et al[4] found that the amyloid fibrils from a patient with laryngeal localized amyloidosis reacted by immunodiffusion with antiserum against κ1 light chain. Amino acid sequencing of 1 peptide showed the protein to be a portion of a κ1 or κ2 light chain with a blocked amino terminus. In addition, the protein contained unusual amino acid substitutions. We now report a more complete sequence of a κ1 light chain protein that was isolated from a localized amyloid deposit found in the larynx.

CASE REPORT

A 63-year-old woman presented to the emergency room of the Boston City Hospital with a history of hoarse voice for 20 years and dyspnea for 2 years

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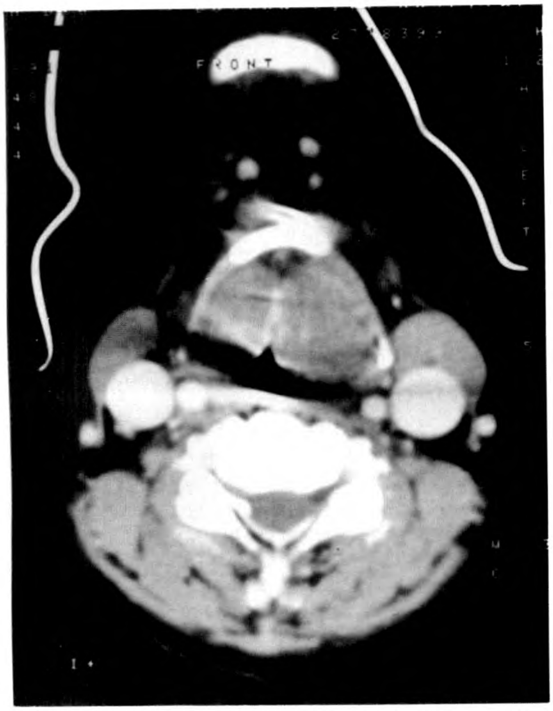

Fig 1. Computed tomogram of neck showing amyloid mass occluding laryngeal airway.

that had progressed to inspiratory stridor. She reported that biopsies had been performed on her throat several years earlier in Vietnam, but the results were unknown. She was immediately brought to the operating room for direct laryngoscopy, which revealed infiltration of the entire laryngeal side of the epiglottis, the false vocal cords bilaterally, the left true vocal cord, the anterior commissure, and both ventricles. There was marked narrowing of the glottic opening. Tracheostomy was performed. Multiple biopsies of the left aryepiglottic fold revealed a large amount of amorphous material that stained positively for amyloid deposits. There was a focal, predominantly plasma cell infiltrate seen within the stroma.

Computed tomography of the neck showed a lobulated supraglottic mass that arose from the left vallecula and broke through the left aryepiglottic fold and crossed the midline to fill both valleculae (Fig 1). The infraglottic airway showed no abnormality. The patient underwent debulking of the mass using a carbon dioxide laser, which has been shown to be useful in the management of tracheal amyloidosis.[14] Tissue at the glottis, anterior commissure, and left true vocal cord was resected.

Extensive laboratory and radiographic evaluation was carried out to exclude systemic amyloidosis. Complete blood count, erythrocyte sedimentation rate, liver chemistries, renal function, urinalysis, and serum and urine protein electrophoresis showed normal results. Findings on chest radiography and electrocardiography were normal. An abdominal fat aspirate was negative for amyloid. A technetium pyrophosphate bone scan was negative except for slight and diffuse uptake in the neck anteriorly, consistent with the patient's amyloid tumor.[15] A technetium pyrophosphate cardiac scan and a gated blood pool scan, known to be sensitive in detection of cardiac amyloid,[16] were negative.

The patient's postoperative course was complicated by aspiration and pneumonia. A modified barium swallow study showed delayed swallowing with penetration of the supraglottic larynx by contrast material on attempted swallowing of both solids and liquids. On ingestion of a large amount of liquid, a small amount of contrast was seen at the level of the vocal cords. She required a repeat tracheostomy and a gastrostomy for nutritional support. Two months later, some recovery in swallowing occurred and she was advanced to a regular diet and has done well since.

MATERIAL AND METHODS

Histochemical Studies. The biopsy specimen was fixed in 10% formalin, processed in a routine manner, and stained with hematoxylin and eosin and Congo red. Immunohistochemistry was performed with polyclonal rabbit anti human κ and λ light chain antibodies (DAKO Co, Carpinteria, Calif).

Protein Isolation. Amyloid fibrils were isolated from a sample of tissue weighing approximately 1 g according to published techniques.[17] Tissue was homogenized in 20 mL of saline and centrifuged. The sediment was rehomogenized in citrate buffer and centrifuged, and the process was repeated with citrate followed by saline until the optical density of the supernatant was less than 0.1 at 280 nm. The sediment was then homogenized in water and centrifuged. In contrast to the usual finding, no amyloid fibrils were detected in the thin, uppermost layer of the final pellet by Congo red staining. However, the pellet stained positively with Congo red throughout, indicating that the tissue was largely replaced by amyloid fibrils. Thus, the pellet was dialyzed against distilled water, lyophilized, and used as starting material for biochemical studies.

Protein Characterization. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was performed in 17% gels according to standard protocols[18] using prestained low–molecular weight markers (Biorad, Richmond, Calif) and horse heart apomyoglobin (Sigma, St Louis, Mo). Amyloid samples (1 mg) were incubated in 6 mol/L guanidine overnight at 4°C and subsequently mixed with an equal volume of 2× sample loading buffer and boiled 5

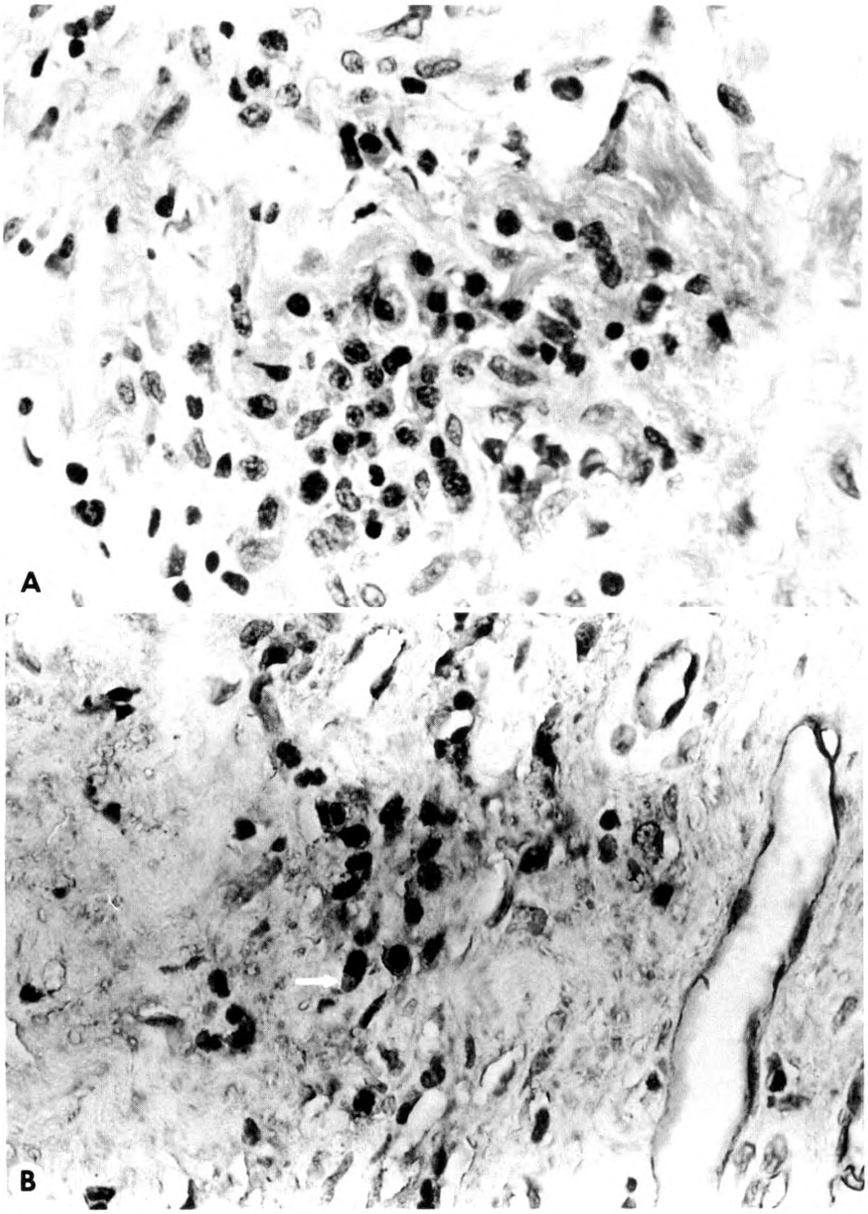

Fig 2. Histologic sections. A) This medium-power view focuses on cluster of benign-appearing plasma cells entirely surrounded by amyloid deposits (H & E, original ×200). Classic morphological features of these cells, including "clock face" nucleus and eccentric cytoplasm, are readily apparent. B) Immunoperoxidase staining for anti-κ light chains shows positive darkening of plasma cell cytoplasm (arrow) and also expected positive staining of background throughout picture (original ×200).

minutes. Approximately 20 μg of protein was applied per lane. Gels were stained with Coomassie brilliant blue R-250 and blotted onto Immobilon-P (Millipore, Bedford, Mass). The major protein peak was sequenced.[19] Sequencing was performed on a 470A gas phase sequencer equipped with a 120 PTH analyzer (Applied Biosystems, Foster City, Calif) by means of program 03R PTH.

Amyloid sample (0.5 mg) was dissolved in 100 μL 8 mol/L guanidine hydrochloride, diluted to 4 mol/L by the addition of 0.2 mol/L ammonium bicarbonate, and digested with trypsin (Worthington, Freehold, NJ) at an enzyme-to-substrate ratio of 1:50 for 4 hours at 37°C. A second equivalent aliquot of enzyme was added and the incubation was continued for another 4 hours. The digest was lyophilized, taken up in 100 μL of 6 mol/L guanidine hydrochloride, and chromatographed on a system with a C18 column (Vydec, Hesperia, Calif) with monitoring at 229 and 254 nm. The column was developed with a 60-minute linear gradient from 100% solvent A (0.1% trifluoroacetic acid in water) to 100% solvent B (0.1% trifluoroacetic acid, 80% acetonitrile, 20% water). Column eluate was collected in Eppindorf tubes in a fraction collector, and tubes containing major peaks (peptides) identified from the ultraviolet scan were sequenced.

Regions in which suspected mutations occurred were examined by reference to known sequences,[20] and compared to sequences in GenBank by means of the FASTA program.

RESULTS

Histologic sections revealed mononuclear and

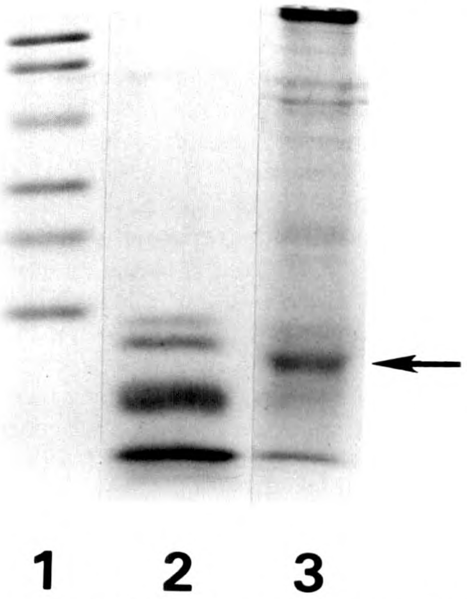

Fig 3. Sodium dodecyl sulfate polyacrylamide gel electrophoresis of amyloid protein from patient. Lane 1 shows molecular weight standards composed, from top to bottom, of phosphorylase b (106 kd), bovine serum albumin (80 kd), ovalbumin (49.5 kd), carbonic anhydrase (32.5 kd), soybean trypsin inhibitor (27.5 kd), and lysozyme (18.5 kd). Lane 2 shows apomyoglobin and derived fragments with molecular weights, from top to bottom, of 17 kd, 14.4 kd, and 10.6 kd, with smaller fragments at tracking dye. Lane 3 shows amyloid protein LLY (20 μg). Shown are 13 kd (arrow), 28 kd, and 44 kd bands, as well as material that did not enter gel. Bands between 44 kd and top of gel are electrophoretic artifacts.

plasma cell infiltration of the submucosa adjacent to and surrounding amorphous acellular deposits of eosinophilic material, consistent with amyloid (Fig 2A). The biopsy specimen was stained with Congo red and showed apple-green birefringence with polarized microscopy. Pretreatment of the specimen with potassium permanganate did not abolish tissue affinity for Congo red stain.

The amyloid deposits and surrounding plasma cells stained positively for κ, but negatively for λ light chains on immunohistochemical analysis with polyclonal antiserum (Fig 2B).

The SDS-PAGE revealed that the washed amyloid sample contained 3 distinct bands with apparent molecular weights of 44, 28, and 13 kd (Fig 3). In addition to these, several other, minor bands were also detected. It is noteworthy that a significant portion of the Coomassie-positive material in the sample did not enter the gel. The 13 kd band from an Immobilon-P blot was subjected to 27 cycles of automated Edman degradation that positively identified this component as the variable region of a κ1 light chain (Fig 4). The Coomassie-positive band at the top of the blot containing protein that did not penetrate into the gel was also sequenced for 5 cycles, and the obtained sequence, NH2-Asp-Ile-Gln-Met-Thr, was identical to the amino terminal 5 residues of the 13 kd protein. Thus, the predominant protein in the amyloid sample was κ1 light chain. It is possible that the 44 and 28 kd bands are multimers of the 13 kd band.

5 10 15
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val

----------------------------N-terminus of 13 kD Band-----------------------

20 25 30
Gly Asp Arg Val Thr Ile Thr Thr Arg Ala Ser Gln Ser Ile Gly

---------------------N-terminus---------------------------------
__________T1__________

35 40 45
Thr Asn Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys Val Pro Lys

_____________T1________________
...................T2...................

110 115
....../ /.....Thr Val Ala Ala Pro Leu Val Phe Ile Phe

ooooooooooooooooooT3oooooooooooooooooooooooo

Fig 4. Amino acid sequence of LLY amyloid protein.

The tryptic digest of the amyloid sample was subjected to high-performance liquid chromatography, and 3 tryptic peptides were sequenced (Fig 4). The positions of peptides in the κ1 light chains were assigned on the basis of homology with known sequences of these proteins.[20] Peptide T1 was sequenced to the carboxyl terminus and was found to correspond to residues 25 through 39 of the protein. Peptide T2 contained 6 residues and corresponded to residues 40 through 45 of the protein. Peptide T3 was sequenced for 10 cycles and could be aligned with residues 109 through 118. Peptide T3 was assumed to be a tryptic peptide because 1) arginine is almost always present at position 108, 2) peptide T3 corresponds to residues 109 through 118 of the constant region, and 3) the predominant protein in the amyloid mass was a κ1 light chain.

In Fig 5, the sequence of the protein from the patient, termed LLY, is compared with that of the only other localized laryngeal amyloid fibril for which sequence data are available, named Wr,[4] and with that of BAN,[21] a prototypical κ1 amyloid protein chain from a patient with systemic amyloidosis, and ROY,[20] a second prototypical κ1 light chain from a patient with myeloma. The first 34 residues of LLY are the first described for a localized laryngeal amyloid, and in residues 35 through 45, LLY differs from Wr at residues 40, 42, 43, and 45. It should be noted that LLY differs from BAN and ROY at numerous positions.

```
                     5                   10                  15
LLY  Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
BAN  ----------- Leu -------------------------------------------
ROY  -----------------------------------------------------------
Wr   BLOCKED N-TERMINUS

                     20                  25                  30
LLY  Gly Asp Arg Val Thr Ile Thr Thr Arg Ala Ser Gln Ser Ile Gly
BAN  --------------------------------------------------- Val Tyr
ROY  ------------------------------- Gln ----------- Asp --- Ser

                     35                  40                  45
LLY  Thr Asn Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys Val Pro Lys
BAN  Asn Tyr Val Ala --- Phe ----------- Pro ------- Ala -------
ROY  Ile Phe --------------------------- Pro ------- Ala -------
Wr                   ------------------- Phe --- Gln Ala --- His/Arg

                      110                 115
LLY  ...../ /.....Thr Val Ala Ala Pro Leu Val Phe Ile Phe
ROY               ------------------- Ser----------------
```

Fig 5. Amino acid sequence of LLY in comparison to those of BAN, ROY, and Wr.

DISCUSSION

This study confirms the immunoglobulin origin of localized laryngeal amyloidosis, which has been suggested in previous studies solely on the basis of immunohistochemistry, but noted by protein sequencing in only 1 case 10 years ago.[4] The cause of localized amyloidosis of the respiratory tract remains unknown. In contrast to systemic amyloidosis, in which little amyloid is found adjacent to plasma cells in the bone marrow (the presumed site of amyloid synthesis), localized amyloid deposits are found surrounded by plasma cells that synthesize immunoglobulin. One theory holds that plasma cells in the tracheobronchial tree produce immunoglobulin in response to an inhaled antigen.[22] Another theory holds that localized amyloidosis results from monoclonal plasma cells that produce either structurally abnormal immunoglobulins or an excessive amount of amyloid that exceeds local clearing mechanisms.

The results of immunohistochemical studies on our report support the latter theory, as both amyloid deposits and plasma cells stained positively for κ light chains. The presence of numerous plasma cells all producing the same type of immunoglobulin may imply a monoclonal origin. If so, localized laryngeal amyloidosis may represent a localized plasma cell dyscrasia analogous to a plasmacytoma, although localized amyloidosis is far more benign and does not progress to multiple myeloma.

The κ1 light chain of LLY contained sequences similar to sequences in both the variable and constant regions. This immunoglobulin was clearly abnormal, consistent with the report of Westermark et al[4] in which an abnormal κ light chain was described in a patient with localized amyloidosis. The sequence of the amyloid protein from LLY reveals unusual amino acid substitutions at 4 positions, each of which can be explained by a mutation in a single base in the codon. The glycine residue at position 30 was described in 2 human κ1 light chain variants,[23,24] 1 of which formed amyloid.[24] The substitution of glycine at position 30 for the more common arginine and serine would require a 1-base change in the codon. It may be that Gly-30 renders the polypeptide more amyloidogenic.

The remaining 3 amino acid substitutions, at positions 32, 40, and 114, have not yet been described to date to our knowledge in human κ light chains. Asparagine at position 32 substitutes for the more common tyrosine and aspartate. Serine substitutes at position 40 for the almost universally conserved proline residue. A substitution at position 40 (phenylalanine for proline) was also found in the only other amino acid sequence described in localized laryngeal amyloid,[4] which also comprised a κ light chain variable region. It is possible that a substitution at position 40 is somehow involved in amyloidogenesis in laryngeal amyloidosis, as this amino acid is almost universally conserved in other known κ1 light chains. It is possible that a substitution at position 40 could substantially change the conformation of the protein, as the substitution of glutamine at position 40 has been described in a patient with Bence-Jones proteinuria and adult Fanconi syndrome, presumably due to the toxic effect of the mutant protein on the proximal renal tubule.[25] The substitution of leucine at position 114 for the more common serine and threonine would require a single base mutation in the codon.

This study suggests that localized amyloid protein has a fibril type similar to that of primary (AL) amyloid. There is no evidence to date that localized amyloidosis can progress to systemic amyloidosis.

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INVERTED PAPILLOMA OF THE MIDDLE EAR

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Inverted papilloma is a benign neoplasm confined almost exclusively to the sinonasal tract. We present the first known case report of an inverted papilloma arising from the middle ear. In this paper we discuss the pathophysiology and review the literature of this interesting clinical entity.

KEY WORDS — inverted papilloma, middle ear, schneiderian papilloma.

INTRODUCTION

We present a 19-year-old woman with primary inverted papilloma of the middle ear. A search of the literature has not revealed any previously reported inverted papillomas arising de novo in the middle ear.

CASE REPORT

A 19-year-old woman presented to our clinic on referral from an otolaryngologist who had discovered and performed a biopsy on a left ear mass 1 month prior to presentation. The patient reported progressive hearing loss in the left ear for 1 year; only with progressive otalgia did she seek medical care. Other than recent development of mild nasal obstruction, she was asymptomatic. She denied vertigo or tinnitus, but had noticed otorrhea since her biopsy. Her medical history was significant for bilateral myringotomy and placement of pressure equalization tubes at age 6, with extrusion of the tubes after 1 year. She denied a history of otorrhea with the tubes.

Her physical examination showed a flesh-colored mass growing through a 20% central perforation of the left tympanic membrane with mild serous otorrhea (Fig 1A). Her right ear was normal. Nasopharyngoscopy of her nasal and upper aerodigestive system showed her nose, nasopharynx, oropharynx, hypopharynx, and larynx to be normal. An audiogram revealed a 30-dB conductive hearing loss and a flat tympanogram in the left ear.

A computed tomographic scan with contrast showed a soft tissue density in the left middle ear filling the hypotympanum, with extension into the entrance of the eustachian tube (Fig 2A). No bony destruction was observed. Fluid was seen in the mastoid tip. A magnetic resonance imaging scan with gadolinium showed an enhancing soft tissue mass of the left ear filling the middle ear and extending into the hypotympanum (Fig 2B). The left mastoid did not enhance, and the right sphenoid sinus was noted to have mucosal thickening. The patient underwent biopsy of the nasopharynx, transseptal sphenoidotomy with biopsy, and tympanomastoidectomy with a facial recess approach. A polypoid mass was found filling the middle ear. The mass arose from a stalk in the protympanum, next to the orifice of the eustachian tube. The mass was noted to encroach upon but did not enter the eustachian tube. The mass was emanating through a 20% central perforation of the pars tensa, with severe thinning of the remainder of the tympanic membrane. The middle ear mucosa was otherwise normal, with no bony erosion. The ossicular chain was intact. The mastoid, attic, and antrum, as well as the nasopharynx, were normal. The sphenoid sinus was found to contain mucus, but the mucosa was normal. A lateral graft using temporalis fascia was used to reconstruct the tympanic membrane.

PATHOLOGICAL FINDINGS

The mass consisted of a thin papillary structure 1.3 cm in length and 3 mm in maximum diameter. The papilloma was attached to the medial wall of the middle ear, adjacent to the opening of the eustachian tube, by a thin stalk 2 mm in diameter. A frozen section was performed of the tissue obtained from the stalk of the polyp, confirming the presence of atypical inverted nests of epithelium. Examination of the hematoxylin and eosin–stained sections showed the presence of irregularly convoluted epithelium varying from squamous to ciliated respiratory (Fig 1B). Additionally, there were scattered intraepithelial glandlike areas filled with mucinous material. The

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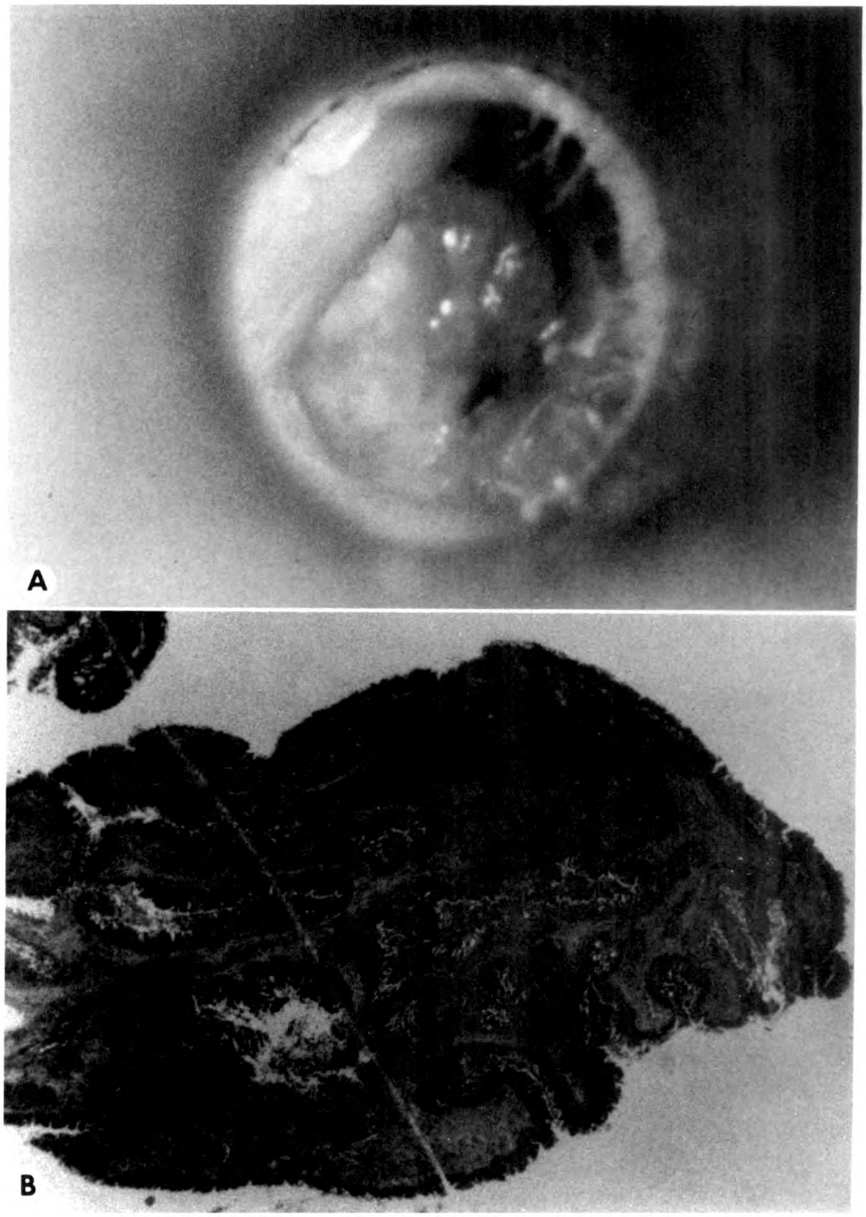

Fig 1. A) Otoscopic view showing polypoid lesion emanating through perforation of tympanic membrane. B) Histologic section showing both exophytic and inverting growth patterns (H & E). Papillary fronds are covered by epithelium that varies from squamous to ciliated.

stroma was well vascularized and mildly edematous, with a chronic inflammatory cell infiltrate. The DNA probe hybridization studies, specifically looking at human papillomaviruses 6, 11, 18, 31, 33, and 35, were all negative.

DISCUSSION

Inverted papillomas (schneiderian papillomas) are the most common benign neoplasm of the nasal mucosa. These lesions occur predominantly in men (2:1 male to female ratio) in the third to fifth decades of life. The inverted papilloma is almost exclusively a lateral nasal wall lesion. A common site is the junction of the antrum and the ethmoid sinus.[1] The biologic behavior of these tumors varies from indolent to locally aggressive, with extension into the adjacent paranasal sinuses, orbit, and cranial cavity.[2] Even with resection, local recurrence is frequent and a recognized complication. Nasal obstruction associated with nasal discharge, epistaxis, and localized pain are the most common clinical presenting features.

Human papillomavirus types 6, 11, 16, and 18 have recently been localized to the epithelium of inverted papillomas in as many as 76% of patients, possibly indicating a new pathogenic mechanism for this lesion.[3,4] As stated above, our DNA hybridization studies were negative.

Historically, the Armed Force Institute of Pathology reports 3 patients with inverted papilloma of the middle ear. However, because of confidentiality regulations, we were unable to obtain data on these patients. All that is known is that 1 patient had several

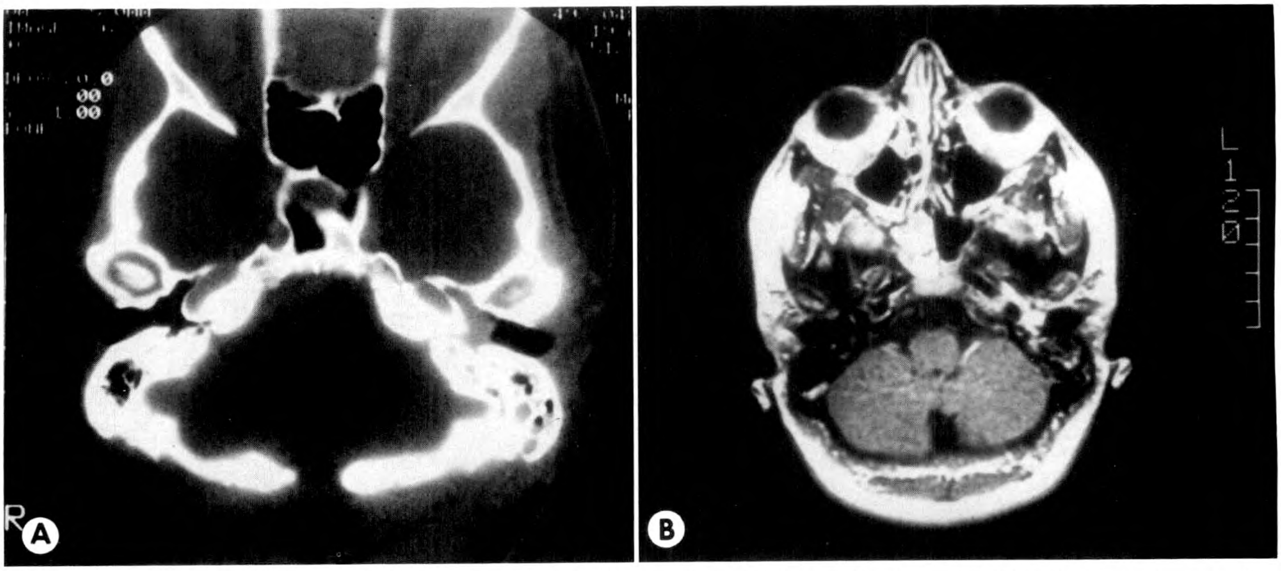

Fig 2. A) Computed tomogram showing soft tissue mass filling middle ear and extending into eustachian tube. Note absence of bony destruction and mucus within sphenoid sinus. B) Magnetic resonance image with gadolinium showing enhancing mass filling middle ear and extending into eustachian tube. Note enhancement of contralateral sphenoid sinus due to fluid.

recurrences over a 10-year period.[5] The only other previously reported inverted papilloma of the middle ear and mastoid occurred in a 55-year-old man who 1½ years prior to admission received a medial maxillectomy for treatment of an inverted papilloma of the right lateral nasal wall and maxillary sinus.[6] The authors of this case report proposed the eustachian tube as the route of transmission. Our patient's nasal and paranasal examination did not reveal any signs of neoplasm. It is unknown if any of the 3 patients from the Armed Forces Institute of Pathology series had a previous nasal inverted papilloma, or if their middle ear papilloma represented a primary lesion.

It is unknown if our patient's prior history of chronic otitis media and myringotomy with tympanostomy predisposed her to or played any role in the development of the inverted papilloma. Metaplastic change from a previous inflammatory polyp has been suggested for the nasal cavity and paranasal sinuses. Similar metaplasia of the middle ear mucosa from chronic inflammation seems possible.

FOLLOW-UP

A second-look exploratory tympanotomy procedure at 1 year did not show any signs of recurrent disease. On a later examination the patient was noted to have anterior blunting of her tympanic membrane. Her audiogram showed a 15- to 20-dB conductive hearing loss in the operated ear, probably secondary to the blunting. Otherwise, she is doing well and is pain-free.

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RAT UTRICULAR MACULA: BLOOD FLOW AND STEREOLOGICAL ASSESSMENT OF CAPILLARY MORPHOLOGY

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Vascular compromise has long been proposed as a cause of inner ear disorders. However, the examination of blood flow and its control mechanisms in the vestibular system has been very limited. Combining stereological techniques with the microsphere injection technique, capillary morphology and regional blood flow were determined for the rat utricular macula. Results are as follows: total utricular blood flow 0.158 ± 0.078 µL/min; blood flow to the neuroepithelium (excluding nerve) 0.0995 ± 0.046 µL/min; blood flow per unit volume 7.71 ± 4.31 µL/min per cubic millimeter; neuroepithelial volume 0.01344 ± 0.0018 mm^3; absolute capillary surface area 0.159 ± 0.039 mm^2; mean capillary diameter 5.84 ± 0.56 µm; absolute capillary length 8.45 ± 1.6 mm; and capillary lumen volume fraction 0.0175 ± 0.004. Comparisons to previous data for the posterior canal ampulla indicate that the capillary diameter in the rat utricular macula is smaller; the capillary length is greater; and the end organs are similar with respect to neuroepithelial volume, capillary surface area, and blood flow. The size of the microsphere used in the present study (9.21 µm), in comparison to the mean capillary diameter (5.84 µm) of the utricular neuroepithelium, would indicate that the blood flow data likely represent a minimum value. These findings indirectly indicate that the utricular macula metabolic rate is greater than that of the posterior canal crista, and that there is variation from end organ to end organ in mean capillary diameter.

KEY WORDS — inner ear, microsphere, stereology, vascular system, vestibule.

INTRODUCTION

The belief that diseases of the inner ear are caused by inadequate circulation has led to several different clinical treatment modalities to improve inner ear blood flow.[1] In addition, the suspicion that inner ear disorders such as presbycusis, sudden deafness, and Meniere's disease are caused by vascular compromise has led to extensive studies of cochlear blood flow (CBF) using a variety of direct and indirect techniques.[2] With respect to the vestibular system, however, there have been very few studies examining blood flow.[3,4]

Vascular occlusion studies have shown differences in the susceptibility of individual vestibular end organs to ischemia.[5,6] These may be due to differences in the origin of circulation to the individual vestibular end organs[7,8] and/or in the metabolic rate of the neuroepithelium. With the use of the microsphere technique, which allows determination of blood flow in absolute units in the rat,[2,9] in combination with stereological techniques, which efficiently obtain unbiased, true 3-dimensional data from 2-dimensional section planes, it has been possible to determine the regional blood flow and vascular morphological characteristics of the rat posterior canal ampullary crista.[3] Both of these variables are indirect indicators of tissue metabolic rate.

The goal of the research presented here was to determine blood flow to the rat utricular macula, neuroepithelial volume, capillary surface area, length, volume, and mean diameter, and blood flow per unit volume and to compare these data to those for the posterior canal ampulla. Results indicate that the capillary diameter in the rat utricular macula is smaller than that in the posterior canal ampulla, while the capillary length is greater, and that these end organs are similar with respect to neuroepithelial volume, capillary surface area, and blood flow. Because of the size of the microsphere used in this study, the blood flow to the utricular macula reported here likely represents a minimum value.

METHODS AND MATERIALS

Eleven healthy male Fischer 344 rats (260 to 325 g; 3 to 6 months old) were used in this study. Each animal was anesthetized with 3% chloral hydrate in saline and placed in the supine position. Both femoral arteries and 1 femoral vein were cannulated with PE 50 polyethylene tubing. One arterial catheter was used for blood pressure monitoring (Coulbourn T42-20 pressure transducer connected to an S72-25 transducer coupler type A strain gauge bridge, an L25-12

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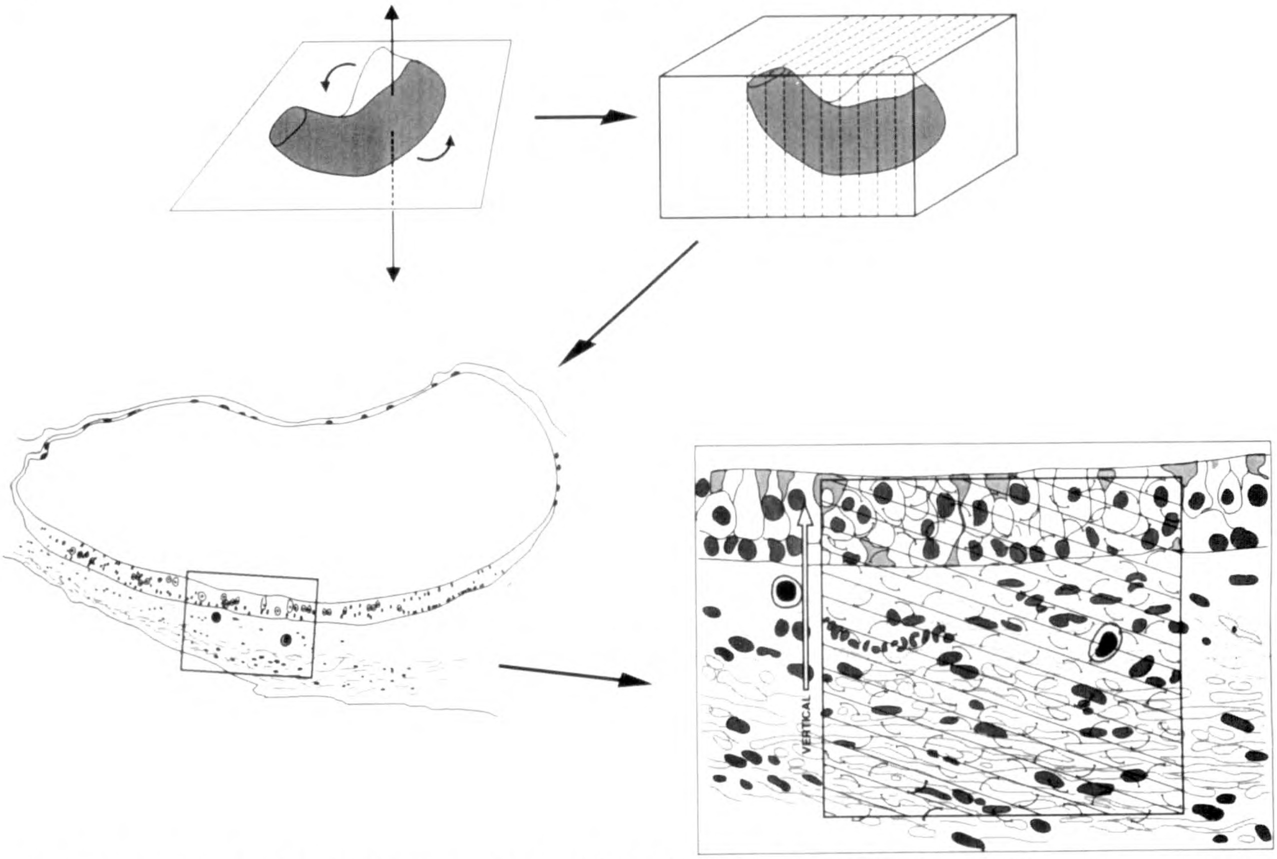

Fig 1. Illustration of "vertical section" technique. In this study, sections used were perpendicular to fixed but arbitrary axis whose direction was designated as side on which nerve enters end organ. System provides 1 *df* around vertical axis (upper left panel) so that sections may be taken on any one of its sides. All sections were cut perpendicular to this axis (upper right panel). Here, random starting point was chosen for first specimen using random number table. Each subsequent specimen was systematically rotated 10° from previous sample. This ensured that each end organ would be sectioned in different orientation to compensate for possibility of nonrandom capillary orientation within specimen. Microspheres, depicted by black dots (lower left), were identified by serially examining sections. Unbiased test system was then used to determine capillary surface area per unit tissue volume by counting intercepts of cycloid arcs with capillary lumen (lower right).

Lab Linc 12 bit analog input module interfaced to an IBM PC using a DATAQ A-D board and software). The other was used for obtaining the arterial blood gas sample (0.3 mL, replaced with 0.3 mL saline, analyzed in a Radiometer Model ABL2 blood gas analyzer, Copenhagen, Denmark) and microsphere reference sample. A rectal temperature probe was inserted (Coulbourn model T31-02 thermistor connected to an S71-30 temperature module) and body temperature was maintained at 37°C.

A transcutaneous injection of cesium 141 microspheres (1×10^7; 9.21 ± 0.53 μm in diameter, specific activity 7.24 mCi/g; 3M, St Paul, Minn; suspended in 1.0 mL saline at 37°C, by sonication), lasting 20 seconds, was made into the left ventricle with a 25-gauge needle and a micromanipulator. Beginning at the time of injection, a 1.0-mL reference sample was taken at a rate of 1.0 mL/min with a syringe pump (Harvard Apparatus model 2200). At 2 minutes, the animals were painlessly sacrificed via an intracardiac injection of saturated potassium chloride and decapitated, and the temporal bones were removed. The bulla and oval and round windows were opened and perfused with 3% glutaraldehyde in 0.1 mol/L phosphate buffer, pH 7.2, and the temporal bone was immersed in this solution for 24 hours. Kidney samples were also taken, fixed in glutaraldehyde, weighed, and gamma counted to document uniform microsphere distribution.

The left temporal bone was decalcified in 10% ethylenediaminetetraacetic acid. The end organs were dissected free, postfixed in 1% osmium tetroxide in the same buffer, dehydrated, and embedded in soft Spurr's embedding medium. With the nerve used as a reference plane (horizontal plane), serial "vertical sections" were cut (Fig 1) at 1 μm and collected on coverslips.

A vertical section is a plane section perpendicular to a given "horizontal" plane. The horizontal plane is only an arbitrary plane of reference defining the orientation of the section. The vertical section technique allows a 3-dimensional structure to be studied

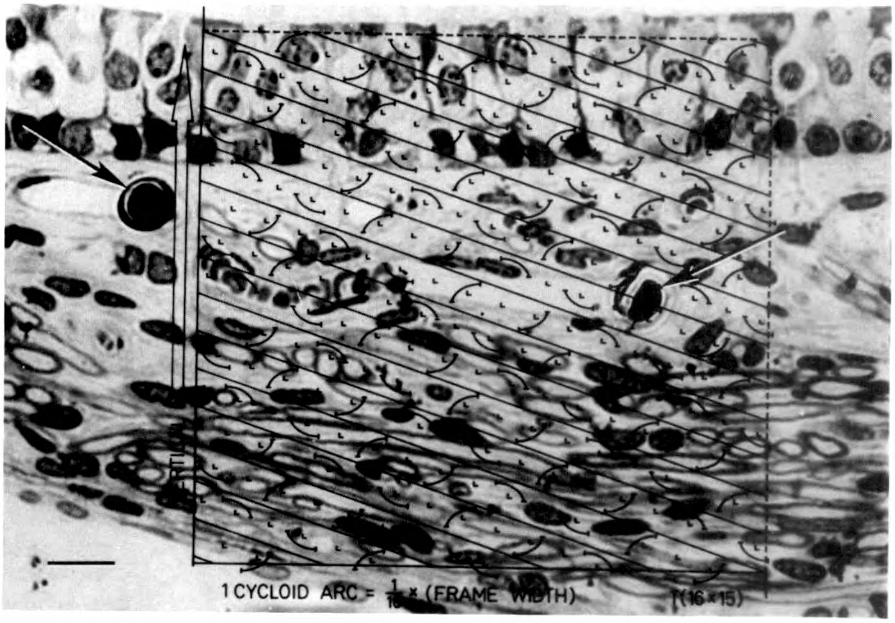

Fig 2. Photomicrograph of cycloid arc test system superimposed on representative 1-µm plastic section of utricular macula. Diagonal lines are only to aid examiner. Hair cells and stereocilia can be seen at top. Arrows — microspheres, calibration bar — 10 µm.

without any assumptions concerning the tissue geometry. This design-based system relies entirely on the manner in which the sectioning is performed, rather than on the precision of an assumed model of the object of interest. Using a test curve (cycloid arc), in conjunction with the vertical sections, allows the sections themselves to become equivalent to an isotropic, random sampling distribution; that is, all surfaces have an equal chance of being intersected by the test probe, the cycloid arc.[10] In this study, the vertical sections used are plane sections, longitudinal to a fixed but arbitrary axial direction designated as the horizontal plane: the side on which the nerve enters the end organ. All sections were cut perpendicular to this axis. The system provides 1 *df* in rotation around the vertical axis, such that sections may be taken beginning on any of its sides. The result is that sections are free to rotate around the vertical axis as long as the 90° angle with the horizontal is maintained. Here, a random starting point was chosen for the first specimen with a random number table. Each subsequent specimen was rotated 10° from the previous sample. This ensured that each end organ would be sectioned in a different orientation to compensate for the possibility of nonrandom capillary orientation within the specimen.

BLOOD FLOW

By counting the number of microspheres in the reference blood samples using a gamma counter (Beckman Instruments, Fullerton, Calif), the total blood flow could be calculated in microliters per minute by a ratio of gamma count results. All sections were serially examined to determine blood flow to the individual end organs by light microscopy surface counting of microspheres.[11] By examining sections considerably thinner than the microspheres, the possibility of a "lost cap" or superposition effect is eliminated.[12] Using this unbiased system, we were able to determine surface area of capillary per unit tissue volume (S_V), volume fraction of capillary lumen (V_{cap}), volume of neuroepithelium (V_{olut}), mean capillary diameter (D_{cap}), and capillary length (L_{cap}).

The test system in Fig 1, consisting of cycloid arcs of known length and number of points, was used to determine the S_V. The system was superimposed on the tissue image (Fig 2) by placing it in a microscope ocular. A systematic random sampling design was used to select sections and section fields.[13] Selected sections were placed on the light microscope under oil immersion at 100×. Systematic random sampling of section fields was achieved with a computer-controlled microscope stage. The arrow at the left of the test system was aligned with the vertical axis of the section. The test system was then positioned to the section's upper left, without being superimposed on the tissue to be sampled. The microscope stage was then offset in the y-axis by an amount randomly generated by the computer. The stage was moved by the computer in uniform increments, in both the x- and y-axes, thus eliminating any overlap between sample fields or operator bias. The volume fraction of the neuroepithelium, excluding the nerve, was estimated by point counting, and the capillary surface area was estimated by counting the capillary lumen intercepts made by the cycloid arcs. The S_V can then be estimating with the formula

$$\text{(1)} \qquad \text{est}S_V = 2\left(\frac{P}{L}\right)\frac{\Sigma I}{\Sigma P}$$

where *L* is the number of intersection points between

TABLE 1. SUMMARY OF INDIVIDUAL ANIMAL BLOOD FLOW AND STEREOLOGICAL DATA FOR UTRICULAR MACULA

Animal	*Volut* (mm^3)	*Sv* (mm^2/mm^3)	*Dcap* (μm)	*Lcap* (mm/mm^3)	*BF* (μL/min)	*Vcap*	*ASv* (mm^2)	*ALcap* (mm)	*BFvol* (μL/min per mm^3)
1	0.01414	14.91	6.59	720	0.0850	0.0246	0.2108	10.187	6.01
2	0.01686	14.26	6.41	702	0.0920	0.0229	0.2404	11.837	5.46
3	0.01292	12.37	5.87	671	0.1234	0.0182	0.1598	8.664	9.55
4	0.01221	10.68	6.43	529	0.1849	0.0172	0.1304	6.453	15.14
5	0.01141	12.61	5.33	754	0.1154	0.0168	0.1439	8.597	10.11
6	0.01453	12.12	5.91	626	0.1171	0.0179	0.1761	9.089	8.06
7	0.01072	9.35	5.09	585	0.1600	0.0119	0.1002	6.270	14.93
8	0.01293	9.50	5.90	512	0.0429	0.0140	0.1228	6.619	3.32
9	0.01574	10.35	4.83	566	0.0780	0.0151	0.1630	8.904	4.96
10	0.01312	11.60	5.92	624	0.0390	0.0172	0.1521	8.186	2.97
11	0.01325	11.51	5.96	614	0.0569	0.0172	0.1525	8.141	4.29
Mean	0.01344	11.75	5.84	628	0.0995	0.0175	0.1590	8.450	7.71
SD(±)	0.0018	1.78	0.56	78	0.046	0.004	0.0390	1.656	4.31

Volut — utricular neuroepithelium volume, Sv — surface area of capillary, Dcap — mean capillary diameter, Lcap — capillary length, BF — neuroepithelial blood flow, Vcap — volume fraction of capillary lumen, ASv — absolute capillary surface area, ALcap — absolute capillary length, BFvol — end organ blood flow per unit volume.

the test lines and the capillary luminal surface, and P is the number of test points hitting the reference space. The ratio of test points (2) to test curve length in real units (microns in this case) is represented by P/*L*. By counting the points of the test grid that fell within the capillary lumen (Pcap) and those that fell within the reference space (Pref), the volume fraction of the capillary lumen was determined by the formula

$$\text{(2)} \qquad \text{Vcap} = \frac{\Sigma \text{Pcap}}{\Sigma \text{Pref}}$$

Mean capillary diameter (Dcap) was determined with the formula

$$\text{(3)} \qquad \text{Dcap} = \frac{4}{\left[\frac{\text{Sv}}{\text{Vcap}}\right]}$$

Assuming that a capillary is a cylinder, the capillary length per unit volume (Lcap) can be determined by

$$\text{(4)} \qquad \text{Lcap} = \frac{\text{Sv}}{2 \times \pi \times \text{r}}$$

where r represents the capillary radius.

The volume of the neuroepithelium (Volut), excluding the nerve, was estimated with Cavalieri's principle.[14] The same section set was used and a point-counting grid was superimposed, covering the entire section at 20×. Each point that fell on the neuroepithelium was counted. Since each point represents a known square area

$$\text{(5)} \qquad \text{Volut} = \text{T} \times \text{Ap} \times \Sigma \text{P}$$

where T is the average distance between sections, Ap is the area associated with each point (real units; square microns) and P is the sum of points taken over all sections. Once Volut was determined, the absolute surface area and absolute capillary length for each end organ were calculated by multiplying the respective per unit volume values by Volut.

STATISTICAL ANALYSIS

The coefficient of error was calculated for each variable by the method of Gundersen and Jensen[13] for systematic sample design, and additional data were collected if $p > .05$. Data were compared statistically to those obtained in a previous study of the posterior canal[3] (animals 1 through 8) and from 3 animals from the present study by a 1-way analysis of variance[15] (BMDP Statistical Software, Los Angeles, Calif). The equality of variance was also tested by Levene's test, and when the null hypothesis was rejected, the Welch Brown and Forsythe tests were used. A probability of $p \le .05$ was set as the level of all hypothesis testing.

RESULTS

Anesthesia, surgery, and microsphere injection were tolerated well by all animals. The mean arterial blood pressure and blood gas chemistries remained within normal limits for anesthetized animals (mean blood pressure 76.4 ± 11.7 mmHg, pH 7.394 ± 0.019, P_{O_2} 87.2 ± 3.2 mmHg, P_{CO_2} 42.6 ± 2.0 mmHg, and hemoglobin 19.4 ± 0.87). Uniform distribution of microspheres was demonstrated by kidney blood flow measurements (4.23 ± 0.94 μL/mg per minute on right; 4.49 ± 0.64 μL/mg per minute on left).

Microspheres were easily identified in the utricle sections, even at low power (20×), and were followed over several sections, providing confirmation of a microsphere since section thickness (1 μm) was less than sphere diameter (9.21 ± 0.53 μm). Total blood

TABLE 2. SUMMARY OF INDIVIDUAL ANIMAL BLOOD FLOW AND STEREOLOGICAL DATA FOR POSTERIOR CANAL

Animal	*Volpc* (*mm*^{3})	*Sv* (*mm*^{2}/*mm*^{3})	*Dcap* (μ*m*)	*Lcap* (*mm*/*mm*^{3})	*BF* (μ*L*/*min*)	*Vcap*	*ASv* (*mm*^{2})	*ALcap* (*mm*)	*BFvol* (μ*L*/*min* per *mm*^{3})
1	0.0131	7.14	10.74	212	0.0520	0.0192	0.0935	2.777	3.969
2	0.0137	8.49	10.70	253	0.0510	0.0227	0.1163	3.466	3.723
3	0.0193	9.71	7.77	398	0.1270	0.0188	0.1874	7.681	6.580
4	0.0074	16.22	9.16	563	0.0880	0.0372	0.1200	4.166	11.892
5	0.0157	13.04	8.24	504	0.0770	0.0269	0.2047	7.913	4.904
6	0.0129	14.05	8.34	537	0.0430	0.0293	0.1812	6.927	3.333
7	0.0114	10.18	10.45	310	0.0720	0.0263	0.1161	3.534	6.316
8	0.0113	8.26	11.77	223	0.0830	0.0243	0.0933	2.520	7.345
9	0.0108	15.22	7.34	660	0.0694	0.0284	0.1644	7.126	6.430
10	0.0087	9.75	9.72	319	0.1179	0.0237	0.0848	2.777	13.552
11	0.0088	12.63	5.98	672	0.0484	0.0189	0.1108	5.896	5.514
Mean	0.0121	11.34	9.11	423	0.0753	0.0251	0.1339	4.980	6.687
SD(±)	0.0034	3.04	1.75	172	0.028	0.005	0.0425	2.143	3.269

Volpc — posterior canal neuroepithelium volume, Sv — surface area of capillary, Dcap — mean capillary diameter, Lcap — capillary length, BF — neuroepithelial blood flow, Vcap — volume fraction of capillary lumen, ASv — absolute capillary surface area, ALcap — absolute capillary length, BFvol — end organ blood flow per unit volume.

flow to the utricular macula was 0.1581 ± 0.0783 μL/min, and flow to the neuroepithelium was 0.0995 ± 0.0464 μL/min. The volume of the neuroepithelium, excluding the nerve, was 0.01344 ± 0.0018 mm^3, resulting in an end organ blood flow per unit volume of 7.71 ± 4.31 μL/min per cubic millimeter. The mean absolute capillary surface area was 0.159 ± 0.039 mm^2, with a mean capillary diameter of 5.84 ± 0.56 μm, and a mean absolute capillary length of 8.45 ± 1.65 mm. The volume fraction of the capillary lumen was 0.0175 ± 0.004. The data for the individual animal utricular maculae are presented in Table 1.

Data from the utricle were compared to those for the posterior canal (Table 2) from a previous study[3] with the addition of the posterior canals from 3 animals from this study. A number of differences were noted. The utricular mean capillary diameter and lumen volume fraction are smaller ($p = .0001$ and .001, respectively), and the absolute capillary length is greater ($p = .004$).

DISCUSSION

The microsphere technique has been used for some time now to study CBF in various species and has only recently been used to study vestibular blood flow (VBF).[3,4,16-19] Angelborg and Larsen[4] were the first to report on total VBF. If the data from Angelborg and Larsen[4,16,17] and Angelborg et al[18] are averaged and corrected for the specific gravity of blood (data were presented as milligrams per minute), the total VBF for the rabbit is 41% of the CBF and 29% of the total inner ear blood flow. This is higher than the 24% of CBF and 19% of total inner ear blood flow reported for the guinea pig.[19] While the CBF was not assessed in the present study, CBF data for the rat have been reported.[9] If these data are used in conjunction with the VBF data presented here, and if inner ear blood flow does not vary widely among different rat strains, the total VBF for the rat is 44% of CBF and 31% of total inner ear blood flow — values that are very similar to those reported for the rabbit. These data suggest that while the absolute value of the inner ear blood flow may vary from species to species, the ratio between CBF and VBF remains constant.

The difference between the ratio of CBF and VBF from the rabbit and rat studies as compared to that found in the guinea pig may be due to differences in the amount of tissue used in the analysis. It cannot be determined from Nakashima et al[19] whether the nerves were included in their total VBF data. It is likely, however, that the nerves were not included. In that study, thick slices (approximately 600 to 700 μm) of tissue were used. The dark microspheres would be difficult to see within nerve superimposed over bone or in areas in which the nerve was viewed on end. In addition, there is the possibility of a superpositioning of the microspheres and thus an underestimation of the sphere number.

The only other study of VBF is in the guinea pig.[19] It is difficult to determine actual blood flow values from this study, because the maculae of the utricle and saccule were pooled and all data, for these structures as well as the other end organs, were presented only in a bar chart as percent of total inner ear blood flow. According to the chart, if blood flows to the saccule and utricle are the same, the flow to the guinea pig utricle is approximately 0.078 μL/min, or slightly less than in the rat.

It was not until the microsphere technique was used in combination with stereological techniques that blood flow comparisons on an absolute and per unit volume basis were obtained.[3] As an extension of this previous study, we have used these techniques to examine regional blood flow and vascular morphology in the utricular macula. In comparing these data to those for the posterior canal ampulla, results indicate similar neuroepithelial volumes, absolute capillary surface areas, and blood flows. There was, however, a significant difference in capillary diameter, with the mean diameter for the utricle (5.84 μm) being smaller than that for the posterior canal (9.11 μm). These results for the utricular macula are in agreement with those of Moriguchi et al[20] and Myers et al.[21]

Since the neuroepithelial volumes and capillary surface areas were similar in these end organs and the capillary diameter was smaller in the utricle, it would be expected that there would be greater capillarity in the utricle. This was the case and is reflected in the absolute capillary length's being significantly greater in the utricle (8.45 ± 1.6 mm) compared to that in the posterior canal ampulla (4.98 ± 2.1 mm). The functional significance of this length and diameter difference is unclear. The symmorphesis hypothesis proposed by Weibel,[22] which states, "Structures supporting a function should be no larger than needed to satisfy the functional demand at the limit of performance," is based on data showing a linear relationship between capillaries and mitochondrial volume density in a number of different muscles. If this hypothesis holds true for the vestibular system, then the larger capillary length in the utricular macula indicates greater peak metabolic requirements for it than for the posterior canal ampulla. This in turn would indicate a need for a greater blood flow to meet these metabolic demands. Because of this higher metabolic rate, these data also suggest that the utricular macula would be more susceptible to ischemic damage, confirming the results of Kimura and Perlman.[5,6]

It may seem that the functional significance of the large difference in capillary length between utricle and posterior canal is significantly negated if one considers the differences in capillary diameter. However, the effect of increasing the capillary length within a similar volume, as is the case here, is to decrease the diffusion distance between the capillary and the target tissue, thereby increasing the efficiency of diffusion and/or transport of substances in both directions. While the diameter differences can change blood flow rate, the data presented here indicate that the utricle and posterior canal have similar blood flow rates and that it may even be greater in the utricle, even though the mean diameter of the capillaries in the posterior canal is 56% larger. This lack of difference in blood flow may be related to differences in the distribution of some regulatory mechanisms in one end organ versus the other. For example, casting methods have shown the existence of arteriovenous anastomoses immediately subjacent to the capillary plexus of the guinea pig utricular macula,[23] and none in the posterior crista. Blood flow to the utricular capillary network can thus be locally regulated by altering the flow through the arteriovenous anastomoses. Nothing is known about the variety or types of vasoactive receptors present within the vestibular vasculature. Sympathetic fibers do end on capillaries within the vestibular labyrinth[24-27] and may be related to vascular control. However, no studies have been performed examining this or the effects of vasoactive drugs on VBF.

When 9- or 10-μm microspheres were compared to 15-μm microspheres[28,29] in the rat cochlea, no difference was found in total CBF. However, both studies did conclude that use of the smaller microsphere resulted in more reliable results. In fact, significant differences in regional CBF have been documented, presumably because of differences in capillary diameter within these regions. The use of stereology to determine capillary diameter in the utricle has provided quantitative evidence that microsphere streaming will not occur if smaller-diameter microspheres are used.[28]

While the ideal size of microspheres used in VBF studies has yet to be determined, our assumption was that an appropriate size would be the same as in previous studies of the posterior canal.[3] However, results indicate that there is variation in mean capillary diameter between vestibular end organs. Since the microsphere diameter used in the present study (9.21 μm) was larger than the mean diameter of the utricular capillaries (5.84 μm), the microspheres would be likely to embolize prior to entering the neuroepithelial capillary network, resulting in underrepresentation in the end organ neuroepithelium and an estimation of blood flow at its minimum. This would seem to contradict the symmorphesis hypothesis. As stated above, one would expect a higher blood flow to the utricular macula. While this was not seen, there was a trend toward higher flow in the utricle ($p = .15$).

Our results suggest that in the future, a greater number of smaller-diameter microspheres would be appropriate for studies of utricular neuroepithelial blood flow. If there is as much variation in capillary diameter among the neuroepithelium of the other end organs, then regional VBF studies would have to be performed using microspheres sized appropriately for each end organ, or using a technique other than microsphere injection. Such a technique to examine blood flow, regardless of capillary diameter, is currently under development in this laboratory.

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IMAGING CASE STUDY OF THE MONTH

TECHNETIUM 99M DIMERCAPTOSUCCINIC ACID SCINTIGRAPHY IN MEDULLARY CARCINOMA OF THE THYROID

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Medullary carcinoma of the thyroid (MCT), a tumor arising from the parafollicular cells of the thyroid, is characterized by the secretion of calcitonin and carcinoembryonic antigen. Serologic measurement of these proteins can be used in the diagnosis and monitoring of MCT. The management of patients with histologically proven MCT who have persistent asymptomatic hypercalcitonemia after surgery can be difficult. Pentavalent technetium 99m dimercaptosuccinic acid (Tc 99m[V] DMSA) scintigraphy has recently been described as an imaging modality useful for the localization of clinically suspected recurrent or metastatic MCT. This report describes the use of Tc 99m(V) DMSA to localize cervical metastatic MCT in a patient with persistent postoperative asymptomatic hypercalcitonemia who had no tumor detected on clinical examination. The role of Tc 99m(V) DMSA scintigraphy in the management of patients with MCT is presented.

CASE REPORT

A 54-year-old woman had a left thyroid lobectomy in August 1990 for an asymptomatic left thyroid nodule, which proved to be MCT. In November 1990 her serum calcitonin was found to be elevated at 556 pg/mL (normal range 0 to 19 pg/mL). A completion total thyroidectomy was then performed. No focus of MCT was found in the resected thyroid tissue. Postoperatively the serum calcitonin remained elevated at 400 pg/mL. Magnetic resonance imaging (MRI) of the neck and chest and ultrasound of the neck demonstrated no mass lesions. An excisional biopsy of a palpable left supraclavicular lymph node was performed in June 1991, but no evidence of MCT was seen histologically.

The patient was then referred for evaluation and Tc 99m(V) DMSA scintigraphy. No palpable thyroid gland or cervical adenopathy was detected on physical examination. A repeat serum calcitonin measurement was increased to 550 pg/mL. Whole body Tc 99m(V) DMSA scintigraphy was performed with 5.4 mCi Tc 99m(V) DMSA. The scan demonstrated a small focus of abnormal radiotracer accumulation in the lower neck, to the left of midline, compatible with a focus of MCT (Fig 1). No corresponding masses were seen on MRI of the neck and mediastinum.

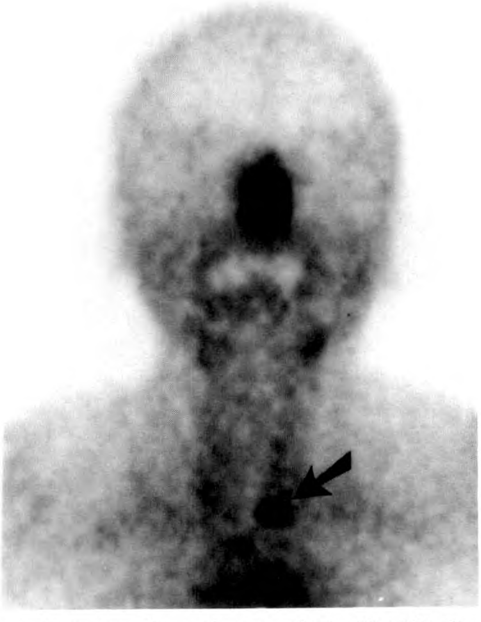

Fig 1. Anterior planar image of Tc 99m(V)–dimercaptosuccinic acid (DMSA) scan. Focus of abnormal radiotracer accumulation is present in lower neck to left of midline (arrow). Nodule (0.8 cm) of metastatic medullary carcinoma of thyroid was identified in left paratracheal lymph node, correlating with abnormal focus on Tc 99m(V) DMSA scan.

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Presented as a poster at the Third International Conference on Head and Neck Cancer, San Francisco, California, July 26-30, 1992.

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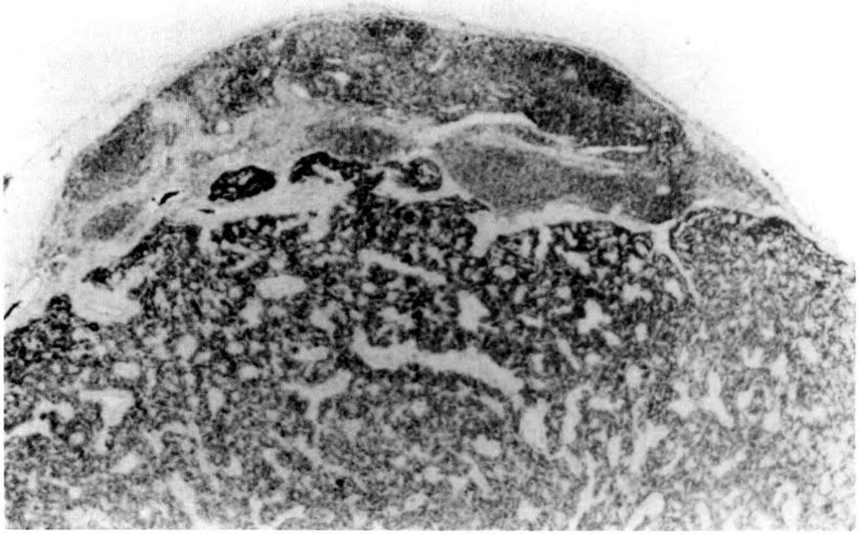

Fig 2. Immunoperoxidase stain for calcitonin. Tumor cells in cervical lymph node stain positive for calcitonin, confirming histopathologic diagnosis of medullary carcinoma of thyroid.

In September 1991 a left modified and anterior selective neck dissection was performed. Intraoperatively, a 0.8-cm firm nodular mass was identified in the left paratracheal tissues. Frozen section diagnosis of the mass was consistent with MCT. The location of the tumor correlated with the area of abnormal uptake in the Tc 99m(V) DMSA scan. Histopathology with immunohistochemical staining for calcitonin confirmed the diagnosis of metastatic MCT in a cervical lymph node (Fig 2). In addition, histopathology identified a 0.2-cm focus of MCT in another paratracheal lymph node and a micrometastasis in one level III cervical lymph node.

One week postoperatively the serum calcitonin had decreased to 71 pg/mL. In November 1991 the serum calcitonin had increased to 120 pg/mL, with no other findings suggestive of recurrent disease. A repeat Tc 99m(V) DMSA scan was performed with single photon emission computed tomography (SPECT) to localize the radiotracer uptake. Whole body scintigraphy using 10.7 mCi Tc 99m(V) DMSA showed mild, diffusely increased radiotracer uptake in the left side of the neck, with the focus of radiotracer seen on the previous scan no longer present. The coronal SPECT images demonstrated two foci of increased radiotracer uptake in the left submandibular region and lower neck, with a linear area of increased radiotracer extending between them (Fig 3). A T2-weighted MRI of the neck, chest, and abdomen demonstrated a diffuse area of increased signal intensity in the region of the left sternocleidomastoid muscle, consistent with either postoperative changes or recurrent tumor. Given the patient's lack of symptoms and mildly elevated calcitonin, the decision was made to continue observation and monitor disease progression with serial calcitonin measurements and Tc 99m(V) DMSA scans.

DISCUSSION

Medullary carcinoma of the thyroid is a malignancy that often follows an indolent course, but is associated with a significant incidence of regional lymph node and distant metastases. Usually occurring in sporadic form, MCT may present in a familial form as a component of the multiple endocrine neoplasia (type II) syndrome. The measurement of high levels of serum calcitonin secreted by the tumor is useful for confirming the diagnosis in sporadic cases, detecting kindred at risk for the hereditary form, and monitoring progression and recurrence of disease.

General agreement exists that treatment for patients with MCT should include total thyroidectomy and resection of the primary-echelon lymphatic tissue. Complete resection of disease will result in a dramatic decrease in the serum calcitonin level postoperatively. As demonstrated by the case presented, persistent or recurrent hypercalcitonemia signifies the presence of MCT. Unfortunately, this serum marker fails to localize the site of tumor, making decisions regarding additional surgical resection difficult, especially in the asymptomatic patient in whom clinical examination does not demonstrate tumor.

To address the problem of localizing persistent and recurrent MCT, a number of radiopharmaceuticals have been studied for the imaging of this tumor. Radioactive iodine, technetium 99m pertechnetate, technetium 99m–tagged phosphates, thallium 201 chloride, iodine 131 metaiodobenzylguanidine, and radiolabeled anti–carcinoembryonic antigen antibody have demonstrated equivocal results as radiolocalizing agents for MCT.[1-3] Selective venous sampling of calcitonin provides an option for localization, but this technique is invasive, time-consuming,

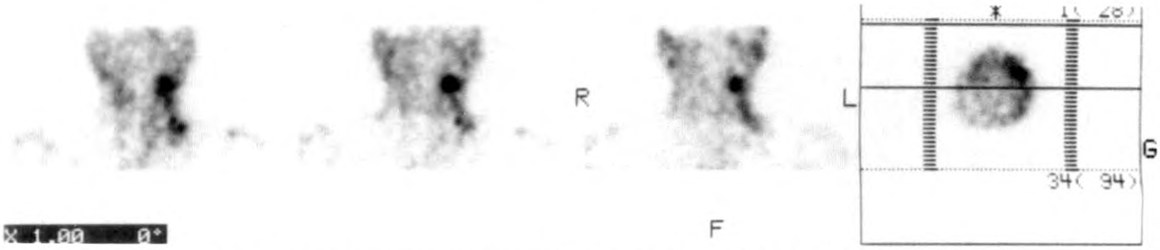

Fig 3. Coronal single photon emission computed tomography image of Tc 99m(V) DMSA scan performed after left modified and anterior selective neck dissection. Increased radiotracer activity is present in left side of neck, extending from submandibular region to lower neck in location of sternocleidomastoid muscle. No palpable mass was evident on physical examination.

and dependent on selection of the correct venous outflow.

In 1984, Ohta et al[4] described the preparation and use of Tc 99m(V) DMSA for the scintigraphic imaging of primary and metastatic MCT. This group reported successful imaging of patients with clinically and radiographically evident primary and metastatic MCT, with no significant accumulation of the Tc 99m(V) DMSA in normal thyroid, salivary gland, or bone, or in other types of thyroid malignancy.[4,5] These findings have been confirmed by others, demonstrating the ability of Tc 99m(V) DMSA to localize primary and locally recurrent MCT, as well as soft tissue and osseous metastases.[1-3,6,7] Although the mechanism of Tc 99m(V) DMSA uptake is unclear, Ohta et al[4] suggested that the agent, which has a technetium orthophosphate core, exhibits characteristics similar to the orthophosphate ion known to accumulate in tumors.

Studies have also demonstrated the diagnostic efficacy of Tc 99m(V) DMSA scintigraphy in detecting suspected persistent or recurrent disease in asymptomatic patients with hypercalcitonemia.[3,8,9] Detection of small-volume disease by this imaging modality has led to early institution of treatment, and afforded the means to monitor the results of therapy. At present, no correlation has been established between calcitonin level and effectiveness of Tc 99m(V) DMSA scanning in this setting. Although Tc 99m(V) DMSA scintigraphy has been shown to detect small foci of MCT with moderately elevated calcitonin levels, false-negative results have been reported.[3,8,9] As in the present case, metastatic microscopic foci may be below the level of detection for this imaging technique. In a review of published results for Tc 99m(V) DSMA scintigraphy, Guerra et al[10] determined the sensitivity and specificity when used for detection of primary MCT to be 77% and 100%, respectively, and 68% and 100% for metastic disease. These investigators found that the addition of SPECT imaging increased the sensitivity above that for planar views. While not ideal, these results are superior to those obtained with other radiopharmaceuticals used to image MCT.[1-3]

The detection of persistent or recurrent MCT by Tc 99m(V) DMSA scintigraphy in an asymptomatic patient with hypercalcitonemia does not necessarily require surgical intervention. Long-term survival is possible in the setting of residual disease with elevated, stable calcitonin levels. One can use Tc 99m(V) DMSA scintigraphy and calcitonin measurement to monitor for disease progression, with directed therapy to specific foci of MCT when indicated. This approach should limit the morbidity associated with undirected extensive surgical exploration in response to hypercalcitonemia alone.[8] The relative ease of preparation, rapid imaging, low radiation dose, high-quality images, ability to combine with SPECT imaging, and efficacy in detecting persistent, recurrent, and metastatic disease make Tc 99m(V) DMSA scintigraphy the recommended choice as a radiolocalizing agent for MCT.

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IMAGING CASE STUDY OF THE MONTH

PURE SECOND ARCH SYNDROME

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High-resolution computed tomography (CT) provides well-defined and increasingly precise illustration of normal and abnormal middle ear ossicles. However, correct analysis of patterns of malformation requires thorough knowledge of normal development. Analysis of clinical observations permits correlation between ossicular malformations and the events of normal and abnormal development.

CASE REPORT

A 16-year-old boy presenting right conductive hearing loss with dysmorphology of the right pinna underwent CT. No familial history of deafness existed, nor other significant malformation. The CT examination was performed with a Somatom Plus (Siemens). The slice thickness was 1 mm in both axial and coronal planes. Sagittal reformations were also performed.

The CT examination displayed an atresia of the external auditory meatus (Fig 1). The middle ear was hypoplastic. A single ossicular mass could be observed at the normal site of the head of the malleus and the body of the incus (Figs 1 and 2). The long process of the incus, the stapes, and the handle of the malleus were absent. The facial nerve had a denuded second part and an anteriorly displaced third part (Fig 2). The inner ear was normal. The styloid process was absent.

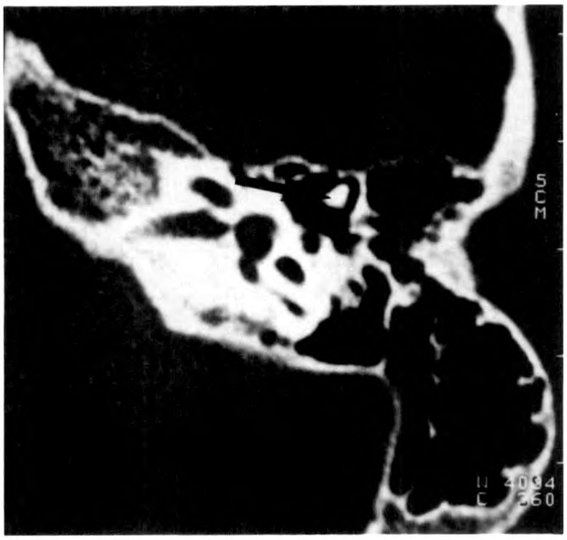

Fig 1. Axial computed tomogram showing single ossicular mass (arrow).

DISCUSSION

The stapes, the enchondral wall of the primitive facial canal, the styloid process, the handle of the malleus, and the body of the incus are considered Reichert's cartilage (second branchial arch) derivatives. The first arch cartilage (Meckel's) gives rise to the head of the malleus and the body of the incus.[1-3]

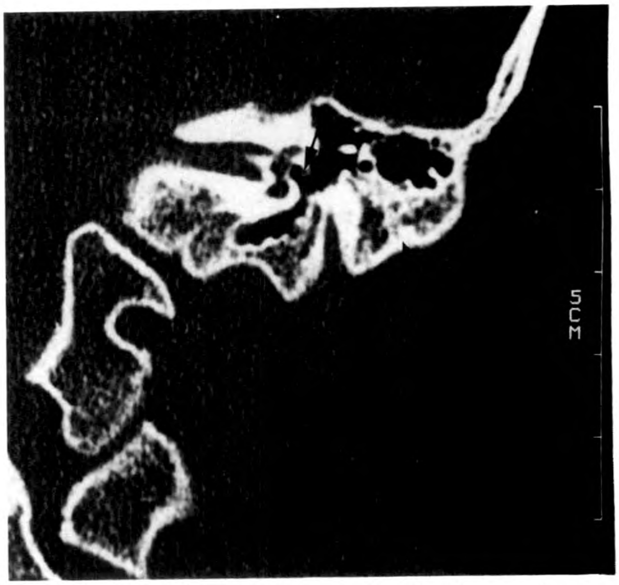

Fig 2. Coronal computed tomogram showing atresia of external auditory meatus (wide arrow), denudation of cranial nerve VII 2 (long arrow), and anterior placement of cranial nerve VII 3 (arrowhead). There is no stapes in front of oval window.

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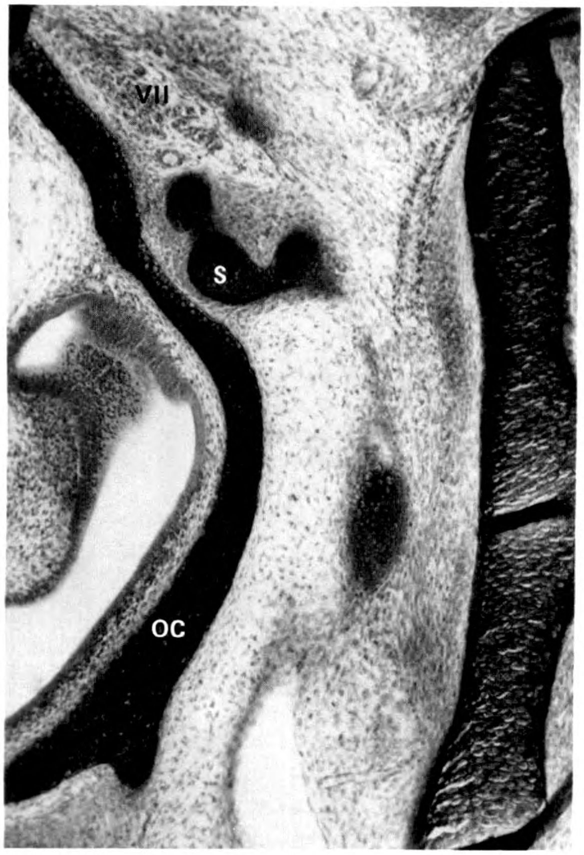

Fig 3. Seventeen-day experimental mouse embryo (see text), frontal 10-μm section (toluidine blue, original ×12.5). Shows abnormally shaped stapes (S) without contact with optic capsule (OC). VII — facial nerve without primitive cartilaginous canal.

Some teratologic models (such as the administration of retinoic acid to pregnant mice) show the persistence of transient connections between the second arch cartilage and its putative derivatives, and also show selective dysmorphologies of the first and second arch–derived structures.[4,5]

Figure 3 illustrates a complex dysmorphology affecting the stapes and the presumptive facial canal in a 14-day mouse embryo whose mother was given 400 mg/kg 13-cis retinoic acid orally on gestational day 9.[5] The stapes is hypoplastic and displays no contact with the otic capsule. The displaced and abnormally shaped Reichert's cartilage does not give rise to the facial canal.

Recently, it was shown that some homeobox genes (which are responsible for embryonic segmentation) are expressed in branchial arches with a very selective pattern, some of them being expressed exclusively in the mouse second branchial arch.[6] According to this finding, it is possible to consider that certain "branchial" human syndromes are due to a possible disruption of some homeobox genes.

The careful analysis of CT features in middle ear dysmorphologies and the comparison of the clinical features with some experimental models can give rise to hypotheses about the possible pathogenesis of congenital anomalies.

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PATHOLOGY CONSULTATION

WEGENER'S GRANULOMATOSIS AND ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODIES

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Serologic tests for antineutrophil cytoplasmic autoantibodies can serve as markers for a number of necrotizing vasculitides and other inflammatory disorders. In the case of Wegener's granulomatosis, an immunofluorescent cytoplasmic pattern and immunoassay for proteinase 3 are quite specific for the disease and are capable of serving as additional criteria for diagnosis. As with any laboratory test, however, results are to be interpreted in the whole clinical and pathologic framework of the disease.

Wegener's granulomatosis is an idiopathic, multisystem disease characterized by a necrotizing vasculitis and necrosis, often with granulomatous, but not granuloma-forming, features. The vascular-based changes may afflict any tissue or organ system, but clinical manifestations are most often those related to involvement of the lungs, upper airway, and kidneys.

The diagnosis of Wegener's granulomatosis has rested on the findings of a biopsy specimen from affected sites, either alone or in conjunction with clinical evidence of systemic involvement.[1,2] Limited forms of the disease, particularly in the sinonasal tract, continue to pose diagnostic problems, and until the early 1980s serologic testing afforded little assistance in differential diagnosis. This changed with the recognition that antineutrophil cytoplasmic autoantibody (ANCA) is a serologic marker for a range of diseases with necrotizing vascular inflammation in patients with renal and extrarenal involvement.[3-6]

Data accumulated over the ensuing years have proven the high immunodiagnostic value of ANCA.[2-8] The association of test results of ANCA with systemic or organ-specific vasculitis varies depending on the organ system studied, and the sensitivity of the testing also varies with the activity and anatomic extent of the disease.[1,2,4,5] The association is also related to 2 distinct cellular immunofluorescence staining patterns: cytoplasmic or C-ANCA and perinuclear or P-ANCA. The C-ANCA, in at least 95% of subjects, is directed against proteinase 3 (PR3), a serine protease found in polymorphonuclear leukocytes and monocytes.[6] The P-ANCA is induced by autoantibodies against a variety of myeloid lysozomal enzymes, especially myeloperoxidase but also elastase, cathepsin, lactoferrin, etc.[4]

While there may be newly discovered antibody specificities of ANCA, there are, at present, only 2 diagnostically informative types of ANCA. These relate to antibodies against the PR3 or myeloperoxidase antigens. Detection systems are 1) indirect immunofluorescence on cytocentrifuged, ethanol-fixed normal neutrophils and 2) antigen-specific immunoassays, eg, enzyme-linked immunoassay.[1,6] As indicated above, there are different staining patterns with the immunofluorescence. The most specific for Wegener's granulomatosis is a fine granular diffuse cytoplasmic fluorescence: C-ANCA. A perinuclear pattern, P-ANCA, is most often seen in non–Wegener's granulomatosis types of vasculitis, but can occur in samples from patients with Wegener's granulomatosis.[3,4,6] A third pattern is nuclear and has no known significance for Wegener's granulomatosis.

The finding of a characteristic cytoplasmic immunofluorescence staining is considered a reliable indicator of the presence of anti-PR3 antibodies, but not all perinuclear or nuclear staining patterns are due to antimyeloperoxidase antibodies.[4,6]

The ANCA associated with pulmonary vasculitis syndromes, including Wegener's granulomatosis, is predominantly cytoplasmic, while a nuclear and perinuclear pattern is found in glomerulonephritis and inflammatory gastrointestinal and "rheumatic" diseases (Tables 1[4] and 2[9]). Between 80% and 90% of P-ANCA in patients with systemic vasculitis or pauci-immunonecrotizing glomerulonephritis has specificity for myeloperoxidase.[6] Other inflammatory diseases may manifest P-ANCA with specificities other than for myeloperoxidase.[6]

It is clear that most patients with pathologic findings considered to be diagnostic of Wegener's

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TABLE 1. ANCA IN VASCULITIDES

	ANCA-Positive	*P-ANCA–Positive*
Wegener's granulomatosis	77% (295/383)	5.2% (20/383)
Polyarteritis nodosa	28.6% (14/49)*	4.0% (2/49)
Churg-Strauss syndrome	30.8% (4/13)†	7.7% (1/13)
Polymyalgia rheumatica	0/62	8.0% (5/62)
Temporal arteritis	0/24	8.3% (2/24)
Behçet's disease	0/21	0/21
Henoch-Schönlein purpura	0/18	0/18
Thromboangiitis obliterans	0/6	0/6
Cryoglobulinemia	0/5	0/5
Unclassified vasculitis	7.3% (8/110)	8.2% (9/110)

Modified from Gross et al.[4]

*Five of 49 were positive for proteinase 3 by enzyme-linked immunoassay.

†One of 13 was positive for proteinase 3 by enzyme-linked immunoassay.

TABLE 2. ANCA-ASSOCIATED INFLAMMATORY DISEASES

	Estimated ANCA Frequency (%)*
Gastrointestinal	
Primary sclerosing cholangitis	80
Ulcerative colitis	75
Autoimmune hepatitis	50
Crohn's disease	15
"Rheumatoid"	
Drug-induced lupus erythematosus	80
Felty's syndrome	30
Systemic lupus erythematosus	15
Rheumatoid arthritis	10

Adapted from Jennette and Falk.[9]

*Predominant immunofluorescence pattern is P-ANCA.

granulomatosis have C-ANCA and anti-PR3 antibodies; ie, C-ANCA is highly specific for Wegener's granulomatosis. In contrast, only a small number of patients demonstrate antimyeloperoxidase antibodies. Fienberg et al[1] indicate that this group of patients segregates, primarily on a clinical basis, into subgroups with other forms of vasculitis: polyarteritis nodosa, microscopic polyarteritis, Churg-Strauss syndrome, polyangiitis overlap syndrome, or primary necrotizing and crescentic glomerulonephritis. Of special importance in classification is the observation that no patient in the study by Fienberg et al[1] had positive tests for both anti-PR3 and antimyeloperoxidase antibodies.

Further affirmation of the specificity of C-ANCA for Wegener's granulomatosis is provided by Nolle et al,[10] who claim a 99% overall association, even in patients with other autoimmune or renal diseases. Jennette and Falk[6] indicate a possible "false-positive" rate of less than 5%.

The sensitivity of the C-ANCA test, however, depends on the extent and activity of the disease. If the manifestations (clinical and pathologic) of Wegener's granulomatosis are limited to the upper or lower respiratory tract, 50% of patients will manifest C-ANCA positivity.[2,5] With increasingly active, generalized disease (higher ELK classes of DeRemee et al[11]), positive C-ANCAs rise to 60% to 100%.[2,5] Despite the lower sensitivity in locoregional disease, the C-ANCA serologic test may facilitate diagnosis before systemic vasculitis occurs.

After establishment of the diagnosis, C-ANCA can be used to assess the activity of the disease and may be helpful in gauging treatment.[2,4,5]

A test with 100% specificity and 100% sensitivity does not likely exist. The C-ANCA test is quite specific and fairly sensitive for active Wegener's granulomatosis. A negative test does not exclude the disease, but a positive test, in the appropriate clinicopathologic context, will practically rule out all upper respiratory tract diseases that can clinically simulate Wegener's granulomatosis.[1,5]

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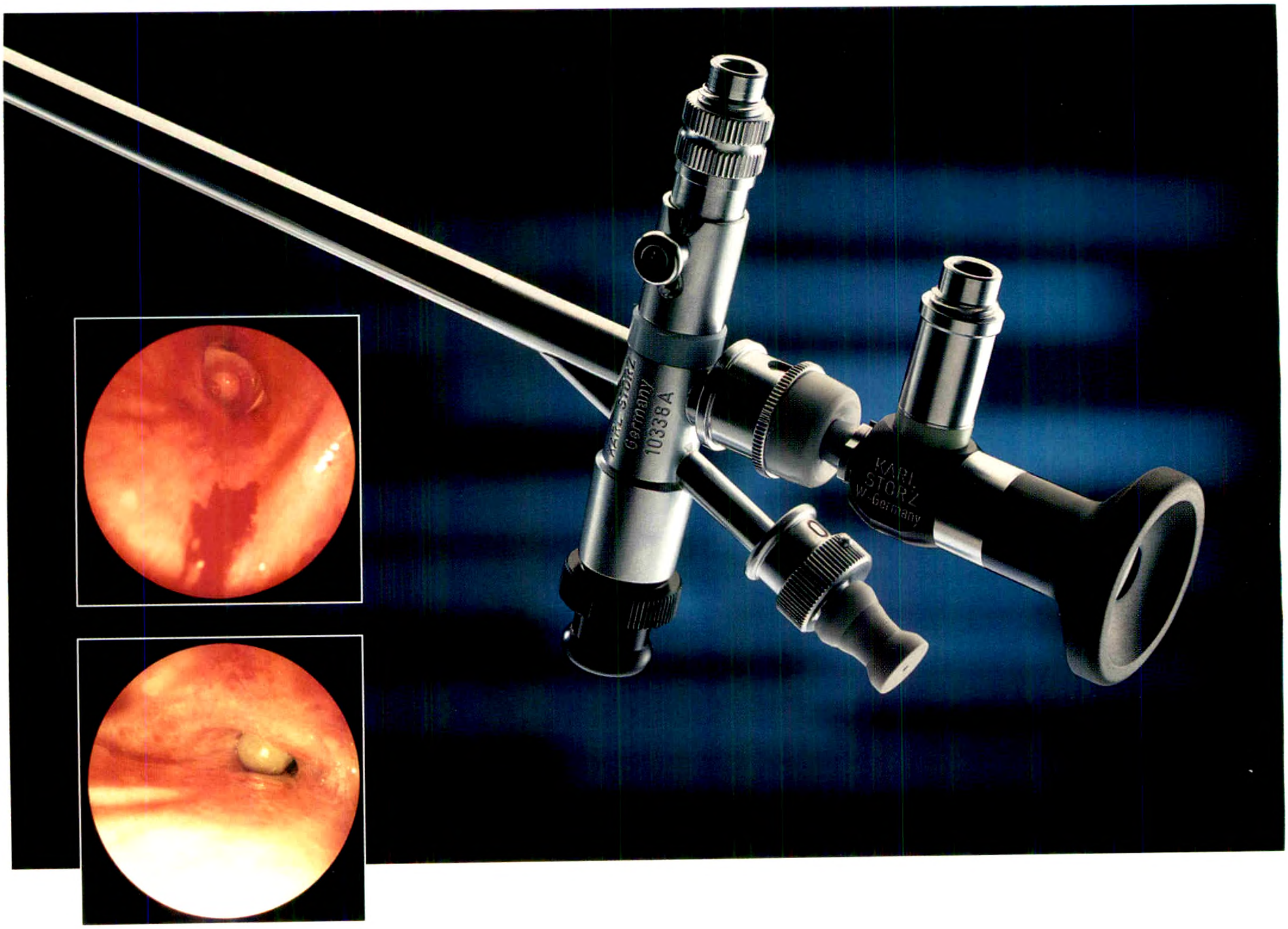

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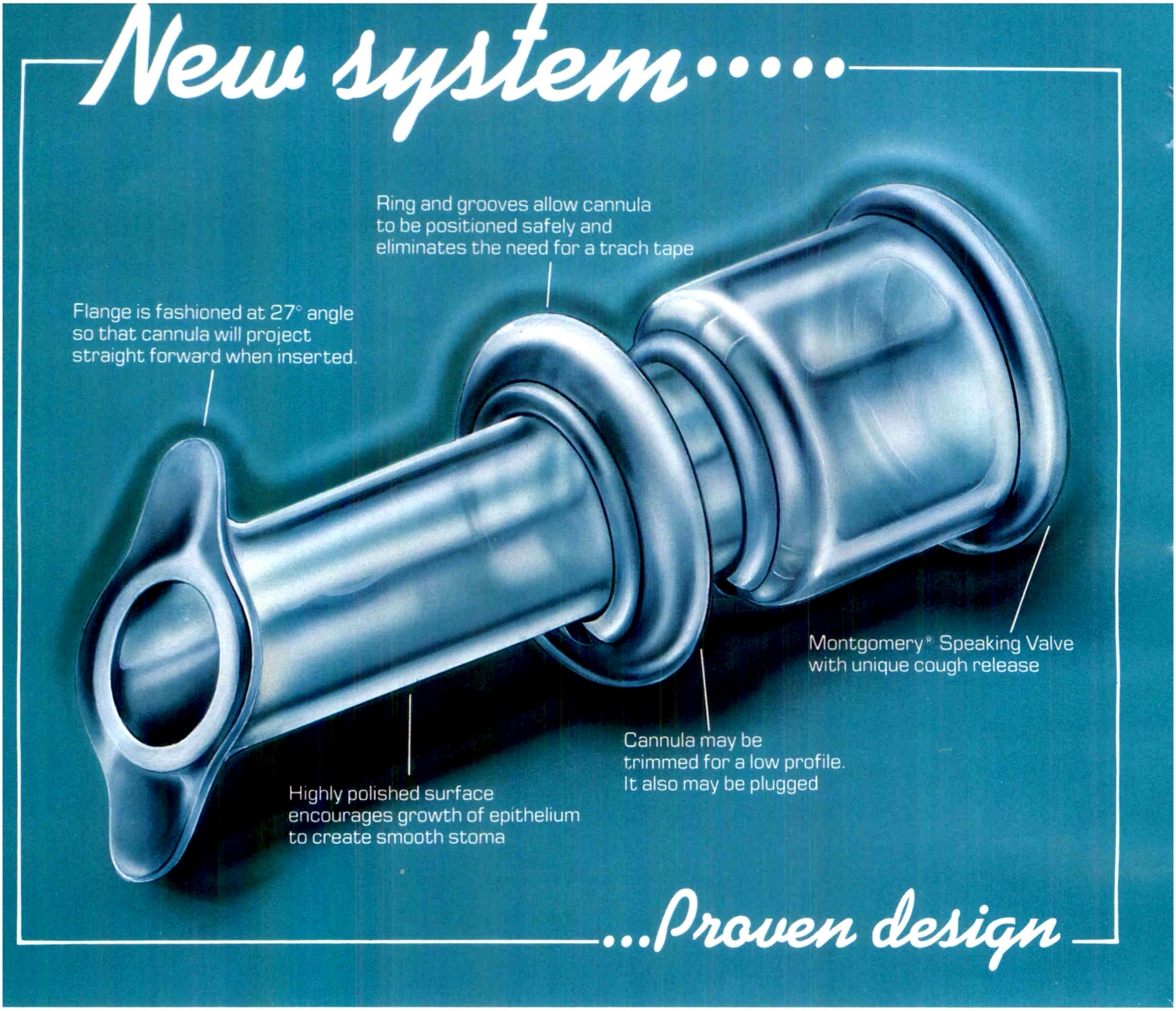
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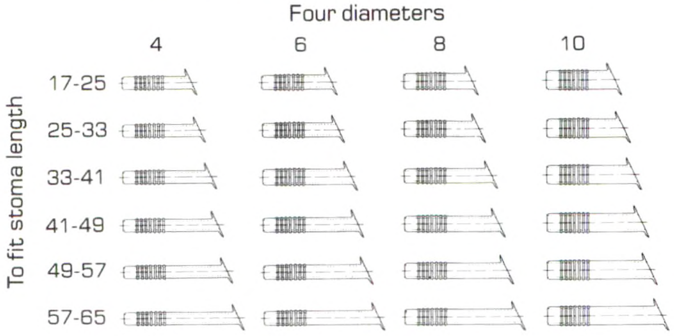

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MULTIVARIATE PREDICTORS OF AUDIOLOGICAL SUCCESS WITH MULTICHANNEL COCHLEAR IMPLANTS

BRUCE J. GANTZ, MD

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IOWA CITY, IOWA

To predict the audiological outcomes of 2 multichannel cochlear implants, a preoperative battery of historical, audiological, electrophysiologic, and psychologic variables from 48 postlingually deafened adults was tested in a prospective randomized clinical trial. Multivariate analyses were used to select and combine these preoperative variables in a predictive index that was significantly related to audiological outcome at 9 months. The preoperative variables included in the predictive index were duration of profound deafness, speech reading ability, residual hearing, cognitive ability, measures of compliance and engagement with treatment, and use of nonverbal communication strategies. The preoperative predictive index had correlations of .81 with the Iowa Sentences Test, and .78 with the NU-6 word understanding scores, both obtained in a sound-only test. Probability and percentile curves generated from these data offer considerable optimism in forecasting the range of likely audiological outcomes that would be realized by postlingually deafened adult candidates for multichannel cochlear implants.

KEY WORDS — cochlear implant, multivariate analysis, predictor variables.

INTRODUCTION

The cochlear implant has become an effective and reliable tool for rehabilitation of profound deafness. The vast majority of postlingually deafened adults and children are able to achieve some sound-only word understanding with multichannel cochlear implant systems.[1-3] Congenitally and prelingually deafened children also are demonstrating some remarkable gains with multichannel devices.[4] Even though dramatic results are realized by some recipients, others achieve only modest benefits. Unfortunately, in the context of extreme variability in outcome, efforts to predict preoperatively the level of performance for the individual implant recipient either have been largely unsuccessful or lack the precision to be clinically useful. Preoperative variables studied, such as cause of deafness, IQ, and response to preoperative promontory stimulation, have not been effective indicators of performance.[1-5] The ability to predict outcome becomes increasingly important as implant systems improve and increase in cost, and implant selection criteria are altered to include patients with more hearing. When considering an implant, it would be highly desirable if the candidate could be informed of the probability and degree of improvement relative to his or her performance with a hearing aid.

One of the primary aims of the prospective clinical trial of different multichannel cochlear implants at The University of Iowa is to develop predictors of audiological success achieved by recipients of multichannel cochlear prostheses. The present report describes a multivariate approach to predicting audiological performance from a set of preoperative historical, audiological, psychologic, and electrophysiologic variables obtained from a sample of 48 consecutively implanted subjects.

METHODS

Subjects. Preoperative and 9-month postoperative data were obtained from 48 consecutively referred adults receiving a cochlear implant in the Iowa Cochlear Implant Research Project. Criteria for inclusion in this research include 1) bilateral profound deafness (pure tone average > 90 dB hearing level [HL]); 2) postlingual deafness (loss of hearing after learning language and scoring within norms established for hearing 10-year-olds on a standardized language test)[6]; 3) word understanding with an appropriately fitted hearing aid of 4% or less on CID W-22 or NU-6 word lists when presented at 60 dB HL; and 4) minimum age of 18 years. Twenty-two women and 26 men ranging in age from 22 to 73 years (mean 52 years; SD 14 years) participated. The duration of their

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From the Departments of Otolaryngology–Head and Neck Surgery (Gantz, Abbas, Tyler), Statistics (Woodworth), and Psychology (Knutson), The University of Iowa, Iowa City, Iowa. This study was supported by research grant DC00242 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders; grant RR59 from the General Clinical Research Centers Program, Division of Research Resources, National Institutes of Health; and the Iowa Lions Sight and Hearing Foundation.

REPRINTS — Bruce J. Gantz, MD, Dept of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

TABLE 1. NINE-MONTH AUDIOLOGICAL PERFORMANCE

Iowa Sentence Test Without Context - Sound Only

	RANGE	MEAN	SD
All Cases (N=48)	0-96%	34%	29%
Nucleus (N=24)*	0-91%	38%	32%
Ineraid (N=24)*	0-96%	30%	26%

NU-6 Word Understanding - Sound Only

	RANGE	MEAN	SD
All Cases (N=48)	0-46%	10%	11%
Nucleus (N=24)*	0-36%	12%	11%
Ineraid (N=24)*	0-46%	8%	11%

* Differences between Nucleus and Ineraid subjects are not significant at P<.05.

profound deafness ranged from 1 to 47 years (mean 13; SD 11). Subjects electing to participate in the research protocol were prospectively randomized to receive either the Nucleus multichannel implant[7] (24 subjects) or the Ineraid (Symbion) multichannel system[8] (24 subjects). The Nucleus implant employs a 21-channel bipolar electrode design to deliver pulsatile information to the cochlear nerve. The coding algorithm used by the subjects in the present study was the F0F1F2 WSP speech processor. The Ineraid cochlear implant is a 4-channel monopolar device. The speech coding strategy used by the subjects in the study was the analog band pass filter paradigm originally developed for the Ineraid system.

Procedure. Candidates meeting the preliminary criteria for receiving a cochlear implant participated in an extensive medical, audiological, electrophysiologic, and psychologic assessment as previously described.[1]

The psychologic battery covered a wide variety of attributes, including intelligence, cognitive abilities, and personality attributes.[9] The research protocol required evaluation prior to implantation and at 1, 9, 18, 30, 42, and 54 months postimplantation. To maximize compliance with the schedule (many of the research procedures required participants to respond to a broad range of test materials), several psychologic factors were included in the final selection criteria, including absence of severe psychiatric illness or personality disorder and measured intelligence above 74 on the Wechsler Adult Intelligence Scale–Revised.

The postoperative audiological assessment was performed uniformly in a sound field at 65 dB sound pressure level. Subjects were allowed to adjust their speech processors to the most comfortable level. Test materials, presented from audiotape or laser videodisc, utilized speakers unfamiliar to the subjects. Only 1 presentation of a test item was allowed and none of these test materials was used during rehabilitation. Tests described in this report were all administered in a sound-only condition. The audiological battery consisted of tests from the Minimal Auditory Capabilities Battery[10] and tests developed at the University of Iowa.[11,12] The test battery measures the ability to recognize environmental sounds and to recognize words in sentences (Iowa Sentence Test Without Context) and in isolation (NU-6 Monosyllabic Word Test). Phoneme recognition was measured with the Iowa Videodisc Medial Consonant Test, the Iowa Videodisc Vowel Test, and the NU-6 Monosyllabic Word Test. Performance in noise was evaluated with the Spondee 4-Choice In Noise Test.

RESULTS

The open-set word understanding of implant recipients after 9 months of implant use is shown in Table 1. With scores ranging from 0% to 96% correct on the Iowa Sentence Without Context Test and from 0% to 46% correct on the NU-6 word list, the variability in outcome is apparent. It is of interest to note that there were no statistically significant differences in speech understanding between the Nucleus and Ineraid implant groups, even though they employ different electrode configurations and speech coding algorithms. It is also of interest that the audiological performance of this prospectively randomized group of subjects is similar to other reported audiological outcomes of multichannel cochlear implants in postlingually deafened adults.[1,2]

The focus of this report is the possibility of predicting audiological performance after 9 months of implant use on the basis of a multivariate combination of preoperative measures. Several different methods may be used for selecting variables in multivariate analyses, each of which can yield somewhat different results. For that reason, the statistical strategies adopted are described in some detail and in the order of completion to clarify the approach for other inves-

TABLE 2. CORRELATIONS[1] OF PREOPERATIVE MEASURES WITH NINE-MONTH AUDIOLOGICAL ASSESSMENTS

	Audiologic Measures[2]						
Predictors	SNT	CNS	NU6 WRD	NU6 PHN	ENV SND	VWL	SPN
HISTORY							
Years Profound hearing Loss	-48	-40	-45	-49	---	-40	-49
Age at Implantation	-34	---	-45	-38	-40	---	---
Etiology	---	---	---	---	---	---	---
AUDIOLOGY							
# of Frequencies w/detectable hearing	37	---	31	---	39	30	---
Pure Tone Thresholds							
250 Hz	---	---	---	---	-53	---	---
500 Hz	---	---	---	---	---	---	---
1000 Hz	---	---	---	---	---	---	---
2000 Hz	---	---	---	---	---	---	---
4000 Hz	---	---	---	---	---	---	---
8000 Hz	---	---	---	---	---	---	---
Sentences (visual)	---	34	35	---	---	39	---
Consonants (visual)	38	44	40	39	48	52	---
ELECTROPHYSIOLOGY (n=29)							
Round Window Stimulation (125 Hz)							
Dynamic Range	35	---	37	37	---	---	---
Loudness Growth Slope	---	---	-35	-37	---	---	37
Gap Detection	---	---	---	-37	---	---	-45
PSYCHOLOGICAL							
CPHI							
Communication Performance							
Social Importance	36	---	37	41	43	43	36
Home Score	---	---	---	---	---	---	---
Home Importance	---	---	---	35	35	34	36
Communication Environment							
Behavior of Others	---	---	---	---	---	---	---
Attitude of Others	---	---	---	---	---	---	---
Communication Strategies							
Maladaptive Behaviors	---	---	---	---	---	---	---
Verbal Strategies	---	---	39	40	40	38	---
Nonverbal Strategies	44	42	40	47	45	---	---
Personal Adjustment	---	---	---	---	---	---	---
Acceptance of Loss	---	---	---	---	---	---	---
Exaggeration of Responsibility	---	---	---	---	---	---	---
WAIS-R (all IQ scales)	---	---	---	---	---	---	---
Ravens Matrices (all scales)	---	---	---	---	---	---	---
Benton Visual Retention Test)	---	---	---	---	---	---	---
Wechsler Memory Test	---	---	---	---	---	---	---
Multilingual Aphasia	---	---	---	---	---	---	---
Beck Depression Index	---	-32	---	---	---	---	---
MMPI							
Scale K	---	---	---	---	---	---	34
Scale 5	---	---	---	---	---	---	---
Scale 9	---	---	---	---	---	---	---
Scale A	---	---	---	-34	---	-34	---
Scale Mac	---	---	---	---	---	-43	-38
Scale Anxiety and Distress	---	---	---	---	---	---	---
Rathus Assertiveness Scale	---	---	---	---	---	---	---
Health Locus of Control	---	---	---	---	---	---	---
Krantz Health Opinion Survey							
Total	51	---	46	43	---	35	---
Information Seeking	36	---	---	---	---	---	---
Behavioral Involvement	53	34	51	47	---	38	34
Cognitive Tests							
Probability Learning Task	---	---	---	---	---	---	---
Signal Detection Score	---	---	37	38	38	41	48
Sequence Completion Task	---	43	34	34	---	41	59

---

1. Correlations accounting for 10% of variance or more are shown ($r > .32$ or $r < -.32$). Not all of these are significant due to reduced sample sizes for some variables.

2. Iowa Laser Videodisc Sentences (SNT) and Consonants (CNS). NU6 Words (WRD) and Phonemes (PHN), Iowa Environmental Sounds Test (SND), Vowel Confusion Test (VWL), Spondee Test (SPN).

TABLE 3. PROPORTION OF VARIANCE[1] OF NINE-MONTH AUDIOLOGICAL BATTERY EXPLAINED SINGLY BY SEVEN PREOPERATIVE PREDICTORS AND PROPORTION OF VARIANCE[2] OF NINE-MONTH AUDIOLOGICAL BATTERY EXPLAINED JOINTLY BY SEVEN PRESURGICAL PREDICTORS

	SINGLE PREDICTORS								JOINT PREDICTORS						
PREDICTORS	SNT	CNS	NU6 WRD	NU6 PHN	ENV SND	VWL	SPN	MEAN[3]	SNT	CNS	NU6 WRD	NU6 PHN	ENV SND	VWL	SPN
Duration*	27	23	26	26	9	20	22	22	27	23	26	26	5	16	22
ILVCT** - Vision	14	19	15	13	22	26	14	17	1	15	9	1	22	26	2
CPHI NVCSS***	17	16	14	18	18	11	9	15	12	8	4	14	11	5	8
VMS****	12	12	10	13	15	17	22	15	6	3	4	12	10	6	19
KHOS+ Total	25	7	20	18	3	12	5	13	19	--	5	8	--	2	--
Number++	15	6	14	10	16	7	1	10	3	1	15	1	3	1	--
RWDR+++	8	6	10	8	0	3	8	6	--	--	1	--	2	--	1
Total[3]									68	51	63	63	53	57	52

* Profound Deafness (log)
** Iowa Laser Videodisc Consonant Test
*** Non-Verbal Communication Strategies Scale
**** Visual Monitoring Score
+ Krantz Health Opinion Survey
+ + Frequencies with Detectable Hearing
+ + + Round Window Dynamic Range (125Hz)

1. Proportion of variance explained in the order of entry of variables under forward selection. All variables predicting above chance are shown.
2. See Table 2 for variable identifications.
3. Proportion of variance (R-Squared) explained jointly by the predictors.

tigators.

The 9-month performance measures to be predicted included the percent correct on the Iowa Laser Videodisc Sentence Test, the NU-6, the Environmental Sounds Test, the Consonant Confusion Test, the Vowel Confusion Test, and the Spondee In Noise Test, all administered in an audition-only format. The first stage in the development of the predictive model was to complete Pearson product moment correlation coefficients between the full set of preoperative variables and these postoperative audiological outcome measures. Predictor variables accounting for at least 10% of the variance in outcome variables (ie, $r > .32$ or $r < -.32$) were retained for inclusion in subsequent analyses. Table 2 shows the correlation matrix of predictor variables and audiological outcome measures. Only the correlations accounting for at least 10% of the variance are presented, but the other variables of interest (eg, cause of deafness and IQ) are presented to demonstrate their negligible correlation with outcome measures.

From the set of preoperative variables that accounted for at least 10% of the variance in outcome measures, a subset of variables was selected that had the most consistently high correlations across the outcome measures and were not redundant with the other variables within the subset (ie, low correlations between pairs of subset predictor variables). This subset of 7 variables was then submitted to a series of multiple regression procedures to select an *efficient* subset of predictor variables. Specifically, an efficient subset was selected by applying Mallow's C_p criterion[13] to the various combinations of these selected variables to obtain the maximally economical subset of variables for predicting the audiological outcome measures. The C_p statistic is used to select a subset of predictor variables by balancing the ability to predict the audiological outcome of the 48 current subjects with a multiple regression equation (multiple R^2) against the reduced predictive power that would obtain in future samples because of statistically selecting useless predictors due to chance in the present sample. Because the C_p statistic is not related in any simple way to significance levels, the actual C_p statistics are not reported here. However, it is important to note that the set of predictor variables selected through the C_p statistic is only one of several approximately equally useful sets of variables. Thus, while the selected set provides an economical predictive model, the exclusion of a variable from the model does not imply that it has no predictive power.

The left panel of Table 3 lists the 7 selected predictor variables and the mean percentage of the variance in the audiological outcome measures explained singly by each predictor variable. The right panel of Table 3 lists the percentage of variance in audiological outcome explained by each preoperative measure when these 7 variables are entered in order

TABLE 4. PREDICTOR WEIGHTS AND STATISTICS

PREDICTORS	WEIGHTS	MEAN	STD DEV	MINIMUM	MAXIMUM
Intercept	-15.45				
Duration	-12.98	2.32	0.90	0.69	3.87
ILVCT - Vision	0.45	28.56	7.80	15.99	49.32
CPHI NVCSS	13.22	4.05	0.70	2.10	5.00
VMS	3.28	0.00	1.43	-4.41	1.58
KHOS Total	1.83	5.58	4.09	0.00	15.00
Number	17.51	0.16	0.37	0.00	1.00

1. Predictor variables are defined in Table 3.
2. The predictive index is computed by multiplying a patient's scores on each of the predictor variables by the weights for those variables, totalling these weighted values and adding the intercept.

in the multiple regression. As shown in the right panel of Table 3, from 51% to 68% of the total variation among subjects on each of the variables in the audiological battery is predictable from preoperative measures. Clearly, the predictor measures vary in their ability to predict audiological outcome. When used singly, the preoperative measure of the dynamic range at 125 Hz, taken at the round window, is, at best, marginally useful in predicting audiological outcomes. In the joint analysis, the measure taken at the round window had no useful predictive power beyond that provided by other noninvasive measures.

From Table 3, it is apparent that the most useful single predictor is the duration of profound deafness expressed as the logarithm. (With a logarithmic transformation, the negative influence of each additional year of deafness declines with the number of years of deafness.) In addition, speech reading ability demonstrated on the vision-only Consonant Confusion Test, the Nonverbal Communication Strategies score from the Communication Profile for the Hearing Impaired (CPHI), a measure of participation and engagement in health care (Total Score from the Krantz Health Opinion Survey), the cognitive ability to accurately identify rapidly changing sequentially arrayed signals (Visual Monitoring Score), and a dichotomous variable indicating the presence or absence of detectable hearing at greater than 4 frequencies all proved useful in combination.

The next step was to reduce the subset of preoperative predictor measures to a single predictive index. Because of the lack of predictive power provided by the measure of dynamic range at 125 Hz assessed at the round window, that variable was deleted. The remaining 6 preoperative predictors were then reduced to a single predictive index by linear regression of the predictors on the optimal monotonic transformation of the Iowa Sentence Test Without Context scores using the TRANSREG procedure of the Statistical Analysis System (SAS).[14] The resulting predictive index for a given subject is a weighted sum of the 6 predictor scores minus a constant. The weighting coefficients for each variable in the predictive equation are shown in Table 4, along with the unweighted means, standard deviations, and ranges of those 6 predictor measures.

The distribution of the predictive index scores is shown in Fig 1. In constructing the index, negative scores were converted to zeroes, and missing values of the predictor variables were replaced by their means. The mean predictive index score was 33.9, with an SD of 24.1. The predictive index scores could be as small as −46, for a subject with the least favorable combination of preoperative predictor scores, and as large as 114, for a subject with the most favorable combination of predictor measures. With obtained scores ranging from −10.3 to 94.2, none of the subjects in the present sample was at either extreme, but there was considerable variability among subjects in their predictive index scores.

To illustrate the relation between the predictive index scores (weighted combination of 6 preoperative measures) and audiological outcomes, Fig 2 shows plots of performance (percent correct) on the Sentences Test and on the NU-6 word list as a function of

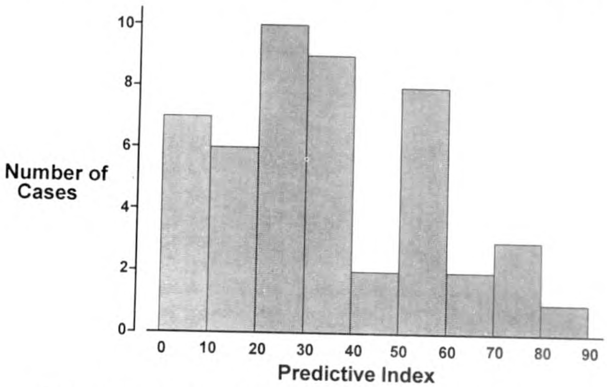

Fig 1. Distribution of predictive index for 48 subjects. Negative values have been replaced by zero.

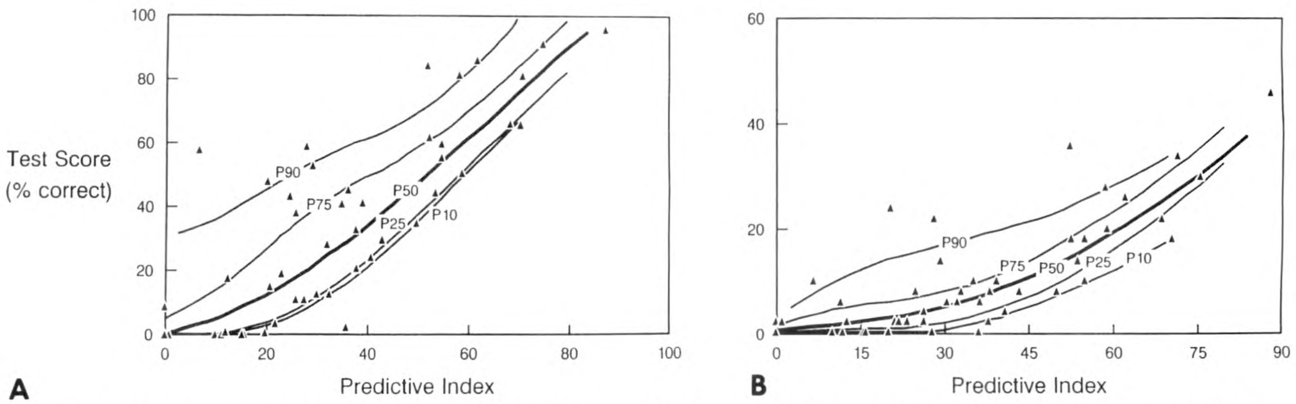

Fig 2. Scores for 48 subjects tested approximately 9 months after connection of cochlear implant. Raw data and smoothed percentile curves are plotted against predictive index. Smoothed percentiles were obtained by fitting monotone splines to moving percentiles by means of 20-case window. P — percentile. A) Audition-only sentence test. B) NU-6 word test.

predictive index scores. It is clear that the predictive index score has considerable utility in forecasting the audiological outcome of the multichannel implants. Superimposed on these plots are smoothed curves at the 10th, 25th, 50th, 75th, and 90th percentiles of actual performance at each predictive score. These curves were obtained by means of a multistage smoothing process from the TRANSREG procedure of SAS.[14] (The smoothing process consisted of detrending the data with a 3-knot monotone quadratic spline, computing moving percentiles by means of a 20-case window, restoring the trend, and then smoothing the retrended moving percentile curve with 2- or 3-knot monotone quadratic splines.) Essentially, these percentile curves indicate the relative performance of implant recipients as a function of their preoperative predictive index. For example, Fig 2A shows that for subjects with a preoperative index of 20, the median predicted performance is about 12% on the Sentences Test at 9 months. Fifty percent of implant recipients with a preoperative predictive index score of 45 achieved 40% correct or greater on the Sentences Test. Ninety percent (10th percentile curve) of the recipients with predictive index scores of 60 achieved scores of 50% or greater on the Sentences Test. Similar information regarding performance on the NU-6 word list is provided in Fig 2B; 50% of the implant recipients with a predictive index score of 45 achieved at least 11% correct on that test.

An alternate way to express the predictability of the audiological outcome scores from the combined preoperative measures is to construct probability curves that indicate the likelihood that a person with a specific predictive index score will achieve at least a given word understanding score after 9 months of experience with a multichannel cochlear implant. Smoothed probability curves for the Sentences Test and the NU-6 word list are presented in Fig 3. (The probability curves were computed by first calculat-

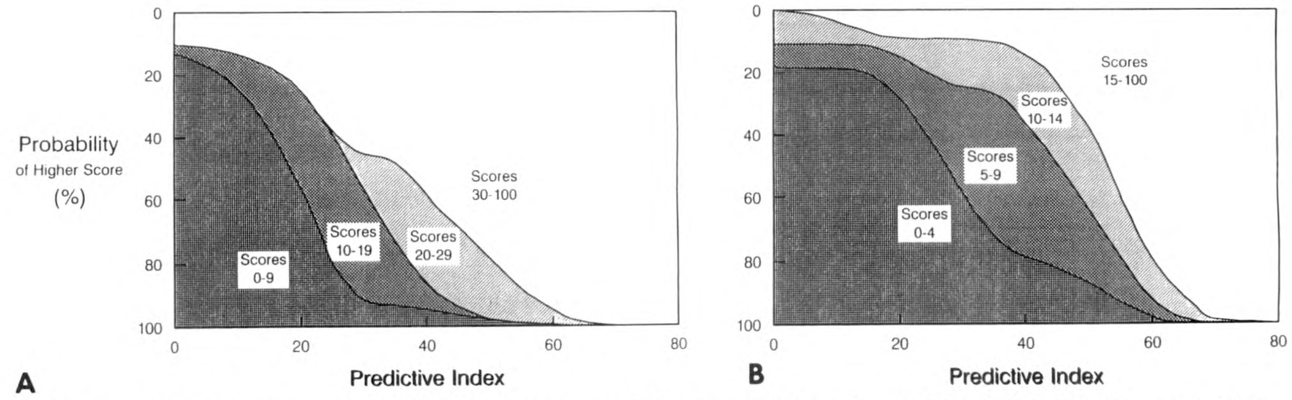

Fig 3. Estimated probability of exceeding given score on particular test administered approximately 9 months after connection of cochlear implant. A) Iowa Laser Videodisc Sentence test administered under audition-only conditions. Probabilities of equaling or exceeding 10%, 20%, and 30% word understanding are plotted as functions of predictive index. Probability curves were obtained by fitting monotone splines to moving success rates by means of 20-case window applied to data of Fig 2A, with success defined as score of 10% or better, 20% or better, or 30% or better, respectively. B) NU-6 test. Probabilities of equaling or exceeding 5%, 10%, and 15% word understanding are plotted as functions of predictive index. Probability curves were obtained by fitting monotone splines to moving success rates by means of 20-case window applied to data of Fig 2B, with success defined as score of 5% or better, 10% or better, or 15% or better, respectively.

ing the frequency of subjects achieving the indicated scores within a moving vertical strip 20 subjects wide; these rough curves were then smoothed with a 2- or 3-knot monotone quadratic spline). An individual implant recipient with a predictive index of 30 has approximately a 90% chance of achieving 20% or greater correct on the Sentences Test, whereas an individual with a predictive index score of 20 has less than a 20% chance of achieving more than 20% correct on the Sentences Test (Fig 3A). Similarly, an individual with a predictive index of 20 has less than a 20% chance of scoring above 4% on the NU-6 word list, whereas an individual with a predictive index of 40 has approximately an 80% chance of exceeding 4% correct on the NU-6 word list after 9 months of implant experience.

DISCUSSION

Invariably, candidates for a cochlear implant inquire about the level of audiological benefit they are likely to realize. One of the more vexing problems confronting those responding to such inquiries is the great variability in outcome characterizing the current generation of implants, coupled with an apparent inability to predict the outcome. Although the consecutively referred sample of the present study provides outcome data that are consistent with the variability reported in other studies,[1,2] the present study offers considerable encouragement that the variability can be understood and even predicted. That is, by completing modern multiple regression analyses of a set of multifaceted preoperative measures, it was possible to derive a predictive index consisting of a weighted linear combination of preoperative variables that could effectively predict the outcomes of successful and unsuccessful implant users. Jointly, 6 preoperative measures accounted for 67% of the between-subject variance in the sound-only Sentence Test scores ($r = .81$) and 61% of the between-subject variance in the NU-6 word understanding scores ($r = .78$). Not only do the results of the analyses indicate that implant outcomes can be predictable, but the probability curves generated from these data offer the possibility of informing postlingually deafened adult cochlear implant candidates about the range of outcomes they are likely to achieve with the present generation of multichannel cochlear implant systems.

It is important to note that the validity of the specific functional relation between the combined preoperative measures and the outcome measures (ie, specific weighting coefficients) must be established through a replication study. However, regardless of the specific weightings, the preoperative variables combined in the predictive index provide a sense of the factors that are probably important in implant success. It is not surprising that duration of profound deafness is a powerful predictor of performance with an implant, since it may be highly correlated with residual auditory nerve viability, and perhaps the integrity of the auditory cortex. Similarly, residual hearing at more than 4 frequencies contributed to the predictive index and probably serves as a nonredundant measure of neural integrity. The present population of implant recipients has a high percentage of subjects with no measurable hearing, or hearing at only 1 or 2 frequencies. As persons with more hearing are implanted, this variable may become an even more important distinguishing factor in audiological outcome.

The poor predictive utility of the preoperative electrophysiologic measures recorded from round window stimulation, including evoked auditory brain stem response threshold and input-output function, was both surprising and disappointing. It was expected that preoperative round window stimulation would yield useful nerve survival information. The failure of the round window stimulation to yield useful predictive information has caused this program to discontinue invasive preoperative round window stimulation for routine implant candidates. Round window stimulation is still performed, however, on implant candidates presenting with severe labyrinthitis ossificans or a history of trauma or retrocochlear surgical procedures.

An important facet of this multivariate analysis was the ability to identify specific psychologic factors that impact on the audiological outcome of cochlear implants beyond the contribution of apparent neural integrity. The ability to extract information from sequentially arrayed signals and rapidly process that information, as measured by the signal detection score from the Visual Monitoring Task, appears to be relevant to word understanding with an implant. It seems likely that the same attentional and cognitive abilities contribute to performance on the preoperative vision-only Consonant Confusion Test and explain why that preoperative measure also predicts audiological outcome. The utility of 2 self-report measures, the Health Opinion Survey and the Nonverbal Communication Strategies subscale of the CPHI, suggests that the level of engagement and participation of implant candidates and their efforts to use a range of communication skills also contribute to the overall outcome of cochlear implants.

Based on the present analysis of 48 consecutively referred implant recipients participating in a prospective randomized clinical trial, it is clear that the great variability among implant recipients is not attributable to differences between two very different multichannel implant systems. The variability within devices is as great as the variability between devices. Thus, the present results call attention to the importance of subject characteristics in determining the audiological outcome of the present generation of cochlear implants. While the present analyses should be replicated, they suggest that the individual differences among implant recipients can be understood and predicted. Moreover, while the analyses and their results should be useful in guiding future considerations in the adoption of candidate selection criteria, they also suggest the utility of using sophisticated multiple regression procedures for attempting to identify the factors determining implant outcome.

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ANEURYSMAL BONE CYST OF THE MANDIBLE

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The aneurysmal bone cyst is a nonmalignant lesion that by expanding disrupts the architecture of the affected bone and destroys surrounding tissue. Developing rarely in the craniofacial region, and more commonly affecting the long bones and the spine, the lesion has characteristic radiographic features but is definitively diagnosed only by pathologic characteristics. Complete surgical excision is used to treat aneurysmal bone cyst, with either curettage or composite resection. Recurrence is common in incompletely excised lesions. Adjunctive cryotherapy reduces the risk of recurrence, and radiotherapy is reserved for nonresectable lesions. The case we report of a young man seen for a large mandibular aneurysmal bone cyst demonstrates the complexity of diagnosing and treating this condition.

KEY WORDS — aneurysm, bone cyst, cryosurgery, curettage, mandibular disease.

INTRODUCTION

In 1950, Jaffe[1] and Lichtenstein[2] first described aneurysmal bone cyst as a distinct clinicopathologic entity when they independently published detailed descriptions of the lesion's clinical, radiographic, and pathologic characteristics. Aneurysmal bone cysts are benign lesions of bone consisting of a septated, cystic cavity filled with non–endothelium-lined, blood-filled spaces.[3] Although the lesion is neither an aneurysm nor a cyst, Lichtenstein believed that "aneurysmal bone cyst" best described the appearance of the multiloculated, preformed vascular channels bordered by a shell of supporting tissue. The term also helps describe what the surgeon often finds at operation — blood welling up into the operative field during exploration of the mass.

As it grows, expanding and destroying the affected part of the bone by direct compression,[4] the lesion characteristically produces a prominent bulging of the affected bone, which eventually erodes the overlying cortex. However, the lesion is usually delimited peripherally by a thin shell of periosteal new bone.[2] Patients rarely complain of pain unless the cyst affects adjacent nerves or its expansion is great enough to impinge on the surrounding joints and soft tissue.[5] Teeth adjacent to the cyst may be displaced, but usually remain vital.[5] About 70% of all aneurysmal bone cysts occur in the spine and long bones, although any bone may be affected.[5,6] Development of the lesion in the craniofacial region is rare, and the mandible is more often affected than the maxilla.[5,6] Aneurysmal bone cysts constitute 1.5% of all non-odontogenic and nonepithelial cysts of the jaws; 1.9% of all aneurysmal bone cysts occur in the jaws.[7] The lesion is believed to occur slightly more frequently in women than in men and affects young people, usually during the first 3 decades of life.

Of the 65 cases reviewed in this report, only 6 were reported in the otolaryngology literature; most reports appeared in the oral surgery literature. Our objective in adding the case described is to familiarize the otolaryngologist with the initial signs and symptoms of as well as the difficulty in diagnosing and treating aneurysmal bone cysts.

CASE REPORT

A 32-year-old man was seen at the head and neck surgery department of the Kaiser Permanente Medical Center, Oakland, Calif, after a 5-week history of an enlarging, painless mass in the left preauricular region. The patient reported mild blunt trauma to the area just before the mass appeared. He had not had recent dental work and did not complain of fever.

A physical examination confirmed a firm, nonfluctuant, nontender lesion measuring 4 × 4 cm located over the ramus of the left mandible. The mass was smooth when palpated; no crepitation was noted. The lesion was visible intraorally and was apparently displacing the tonsil medially. No evidence of facial weakness or dysesthesia was found. A fine-needle aspiration biopsy was done, and dark-red blood was obtained. Culture grew a small amount of *Bacteroides melaninogenicus*; results of cytologic analysis were consistent with granulomatous reaction and inflammatory cyst. Multinucleated giant cells were seen in the aspirated specimen.

The presumptive diagnosis was infected masseteric space hematoma. The patient was given antibiotic and steroid therapy; the lesion was aspirated and

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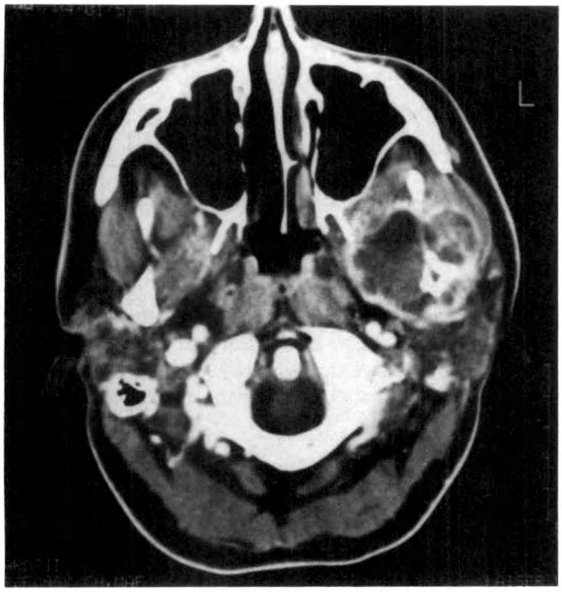

Fig 1. Computed tomography scan clearly showing expansive nature of aneurysmal bone cyst.

drained. Because it was resistant to this therapy, however, open biopsy was done 1 week later, and pathology results were consistent with aneurysmal bone cyst. A computed tomography (CT) scan (Fig 1) performed after the biopsy showed a large, nonhomogeneous mass affecting the left infratemporal fossa by infiltrating and enlarging the left masseter, temporalis, and lateral pterygoid muscles. The mass had eroded part of the ramus; the disease process progressed toward the skull base and laterally to the deep portions of the parotid gland. A plain x-ray film of the mandible (Fig 2) showed marked osseous destruction of the neck and condyle, as well as an associated soft tissue mass in the infratemporal fossa.

Because of the extent of the lesion and because curettage is often curative, conservative surgical therapy was chosen to minimize damage to adjacent vital structures. The patient had 2 major curettage procedures — 1 via the intraoral approach, the second via an extended parotidectomy incision. Bleeding was moderate during curettage. Drains were placed; a cavity then formed, which was treated with frequent packing changes and debridement. The drainage was a mucoid, tan, viscous liquid. Biopsy specimens taken during debridement contained multinucleated giant cells, proliferating fibroblasts, and other elements characteristic of residual aneurysmal bone cyst.

The mass continued to enlarge. The patient complained of severe pain over the mass and in the temporal regions. Total left parotidectomy and partial left mandibulectomy were done. At surgery, the ramus had an "exploded" appearance: spicules of bone were scattered throughout the ramus. The cystic mass appeared to impinge on (but not invade) the surrounding masseter and pterygoid musculature, causing marked edema. The facial nerve was free across the entire surgical cavity of about 5 cm. No mandibular reconstruction was done, and no soft tissue flaps were used. Bleeding from the bed of the debrided area was brisk and tended to well up into the wound. The estimated blood loss was 1,700 mL, but transfusion was not necessary.

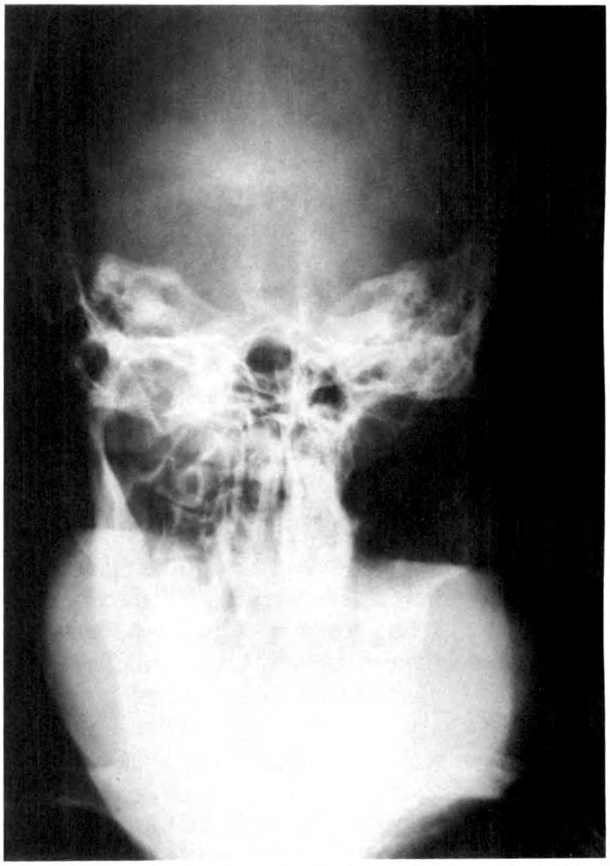

Fig 2. Anteroposterior x-ray film showing characteristic soap bubble appearance.

The resected lesion measured 5.0 × 5.5 × 6.0 cm and was described as cystic, surrounded by skeletal muscle, and having a thin, eggshell-like calcific shell. The lesion's multiple loculi were separated by tan membranous tissue; the cystic spaces were filled with bloody fluid. Histologic examination showed plump spindle-shaped cells and multinucleated giant cells within an eosinophilic fibrous stroma, as well as focal osteoid production (Fig 3A). Vascular channels were filled and dilated with blood and serum (Fig 3B). After surgery, the patient had left peripheral seventh nerve palsy that has resolved with some residual contracture and synkinesis. The patient resumed employment as a sheet-metal worker and had no evidence of recurrent disease 2 years after surgery. A heavy beard masks the surgical defect.

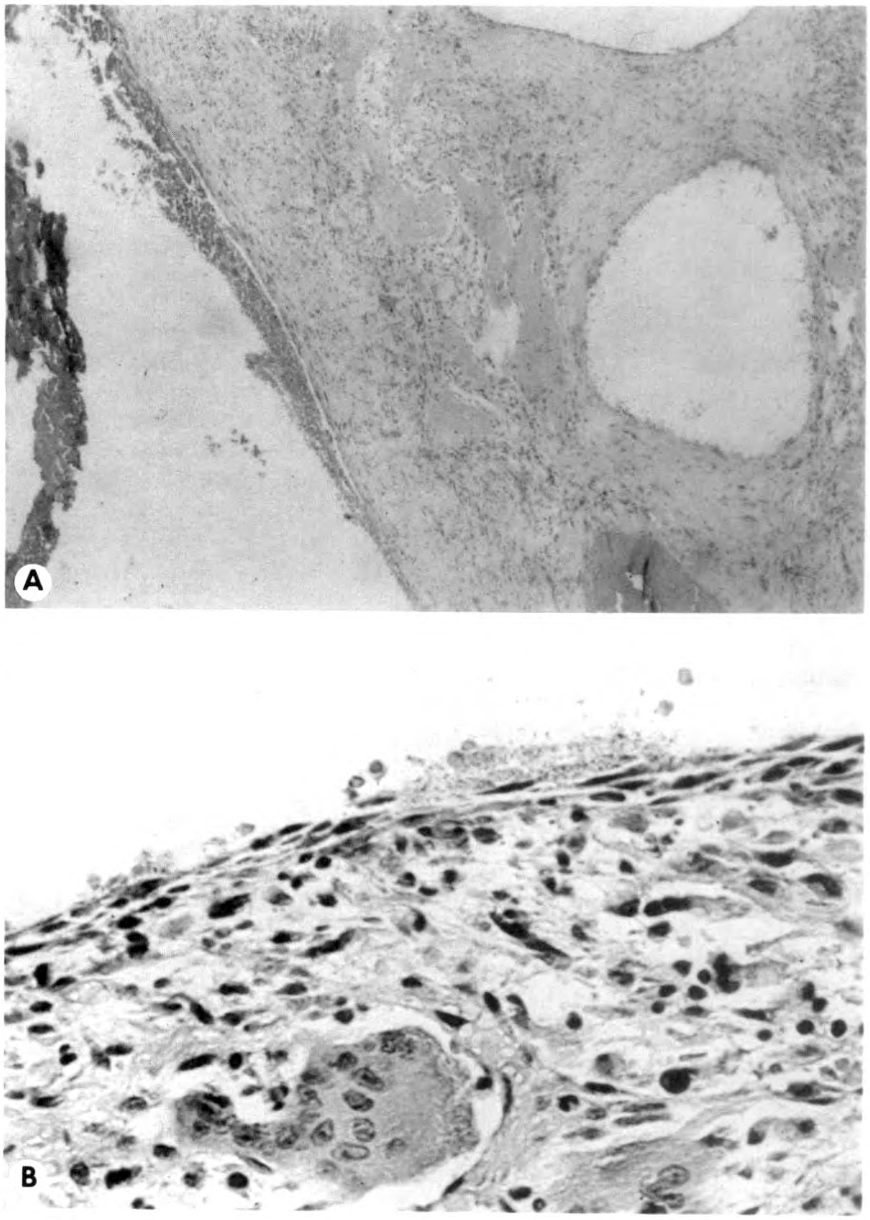

Fig 3. Photomicrographs. A) Low-power, showing large vascular spaces, background of connective tissue, and osteoid formation. B) High-power, showing characteristic endothelial-lined vascular channel, multinucleated giant cells, and spindle-shaped cells.

DISCUSSION

Review of Literature. The Table[4-54] lists the 65 cases of aneurysmal bone cyst of the jaw reported to date. Reports by Bertrand et al,[55] Ruiter et al,[56] Biesecker et al,[3] and Struthers and Shear[57] were excluded, because they contained insufficient clinical information. The mandible was affected in 42 (65%) of the cases, and the maxilla in 23 (35%). The sex distribution was nearly even: 51% of patients were men; 49% were women. Patient ages ranged from 4 to 59 years; the mean age was 19 years. Further investigation of age showed that 70% of patients were age 20 years or younger, and 88% were age 30 years or younger. Analysis by site affected within the mandible when the patient was first seen was done for the 32 patients on whom data were sufficient to determine which sites were then affected. Several cysts were large and affected more than 1 part of the mandible; 43 anatomic sites were examined. The cyst location was the body of the mandible in 17 cases (40%); the ramus in 13 (30%); the angle in 8 (19%); the symphysis in 4 (9%); and the condylar process in 1 (2%). These results are similar to those of Giddings et al,[6] who also found that the most frequently affected area was the body of the mandible, followed by the ramus, the angle, and the symphysis.

Follow-up data were sufficient for reporting in only 43 cases. Sixty-two procedures were done; disease recurred in only 19 patients (31%). In 42 cases, the cyst recurred during the first year after treatment. In 1 patient, the cyst recurred 3 years after treatment.

Simple curettage was the procedure used in most cases (54%), but was associated with the highest

ANEURYSMAL BONE CYST

Authors	*Year*	*Sex*	*Age*	*Site*	*Treatment*	*Follow-up*
Potts[8]	1940	M	6	Mandible	Resection	No recurrence (2.5 y)
Sherman and Soong[9]	1957	NR	9	Mandible	NR	NR
Bernier and Bhaskar[10]	1958	F	11	Mandible	Curettage	No recurrence (1.25 y)
		F	59	Mandible	Curettage	NR
Bhaskar et al[11]	1959	F	9	Mandible	NR	NR
		M	7	Mandible	NR	NR
		F	22	Maxilla	NR	NR
Wang[12]	1960	F	8	Maxilla	Curettage	No recurrence (5.5 y)
Vianna[13]	1962	M	18	Maxilla	Curettage, irradiation	NR
Ebling and Wagner[14]	1964	M	19	Mandible	Resection	NR
Yarington et al[15]	1964	F	48	Maxilla*	Resection	No recurrence (8 mo)
Koticha[16]	1965	F	20	Mandible	Resection	No recurrence (6 mo)
Kagan and Klimova[17]	1965	NR	NR	Mandible	NR	NR
Ostrowski and Tyszkiewicz[18]	1968	NR	NR	Mandible	NR	NR
Nobler et al[19]	1968	M	4	Mandible	Resection	Recurrence at 2 mo, treated by resection; no recurrence (12 y)
Gruskin and Dahlin[20]	1968	M	20	Maxilla	Hemimaxillectomy	No recurrence (26 y)
		F	8	Mandible	Curettage	No recurrence (11 y)
Hoppe[21]	1968	F	12	Mandible	Resection	NR
Nosaka and Nakazana[22]	1968	M	8	Maxilla	Resection	Recurrence, treated by irradiation
Byrd et al[23]	1969	F	17	Maxilla	Curettage	NR
Costas and Pietropinto[24]	1970	F	22	Mandible*	Curettage	NR
LeJeune and Bordelon[25]	1970	F	17	Maxilla	Curettage	No recurrence (3 y)
Daugherty and Eversole[26]	1971	M	17	Mandible	Curettage	No recurrence (6 mo)
Buraczewski and Dabska[4]	1971	F	26	Mandible*	Hemimandibulectomy	Recurrence at 10 mo, given radiotherapy
Lucas[27]	1972	M	29	Mandible	Curettage	No recurrence (3 y)
Ellis and Walters[28]	1972	M	17	Maxilla*	Curettage	NR
Romaniuk and Becker[29]	1972	M	10	Maxilla	Curettage	No recurrence (4 mo)
		F	14	Mandible	Curettage	Recurrence at 1 and 2 y after curettage; resected; recurrence 1 yr after resection, treated by curettage; no recurrence (1.5 y)
Komorn[30]	1972	F	26	Maxilla	Resection	NR
Oliver[5]	1973	F	20	Mandible*	Curettage	NR
Berry et al[31]	1973	M	18	Mandible	Curettage	NR
Powell and Glaser[32]	1975	M	16	Maxilla/orbit	Excision	No recurrence (3 y)
Serrano Roa[33]	1975	M	12	Maxilla	Curettage	NR
Gaillard et al[34]	1976	F	9	Mandible	Curettage	Recurrence at 4 and 10 mo, treated by curettage and drainage; no recurrence (2.5 y)
Eveson et al[35]	1978	F	17	Zygomatic arch	Curettage	Recurrence at 7 mo, treated by excision; no recurrence (9 mo)
Cornyn and Morris (unpublished)	1978	M	10	Maxilla*	Curettage	Two recurrences: after curettage, treated by partial maxillectomy
Reyneke[36]	1978	M	18	Maxilla	Curettage	NR
Hillerup and Hjørting-Hansen[37]	1978	F	10	Mandible	Curettage	Recurrence at 3 y, treated by curettage; no recurrence (3 y)
Boyd[38]	1979	M	27	Maxilla	Curettage	No recurrence (1 y)
		M	23	Mandible	Resection	No recurrence (10+ y)

NR — not reported.

*Aneurysmal bone cyst associated with primary bone lesion.

ANEURYSMAL BONE CYST (continued)

Authors	*Year*	*Sex*	*Age*	*Site*	*Treatment*	*Follow-up*
Steidler et al[39]	1979	F	21	Mandible	Curettage	No recurrence (2 y)
Kane[40]	1979	M	14	Maxilla	Resection	No recurrence (5 y)
Sastry et al[41]	1979	NR	NR	Maxilla	NR	NR
El Deeb et al[42]	1980	M	19	Mandible*	Curettage	Three recurrences, treated by radical curettage; no recurrence (2 y)
Saltzman and Jun[43]	1981	F	22	Mandible	Excision	Recurrence, treated by curettage and cryotherapy; no recurrence (11 y)
Salmo et al[44]	1981	F	55	Bilateral maxilla	Curettage	No recurrence (5 y)
Ueno et al[45]	1982	F	13	Mandible	Hemimandibulectomy	No recurrence (2 y)
Lovely[46]	1983	F	14	Mandible	Curettage	Recurrence at 11 mo, treated by resection; no recurrence (4 y)
Hempenstall et al[47]	1984	F	24	Mandible	Curettage	No recurrence (1.5 y)
Pankey et al[48]	1984	M	NR	Mandible	Embolization, resection, graft	No recurrence (5 mo)
Gingell et al[49]	1984	M	11	Maxilla	Curettage	No recurrence (2 y)
		M	30	Mandible	Curettage	No recurrence (5 y)
		M	14	Mandible	Resection	No recurrence (4 y)
		F	13	Mandible	Curettage	No recurrence (6 mo)
Robinson[50]	1985	M	13	Maxilla*	Resection	No recurrence (2 y)
Okuyama et al[51]	1985	M	6	Mandible	NR	NR
		F	12	Mandible	NR	NR
Zachariades et al[52]	1986	F	35	Maxilla	Curettage	No recurrence (2 y)
		M	37	Mandible	Curettage	No recurrence (4 y)
Eisenbud et al[53]	1987	M	48	Mandible	Irradiation	Recurrence 9 mo after irradiation; no recurrence 17 y after resection
Newman[7]	1987	F	17	Mandible	Curettage	NR
Toljanic et al[54]	1987	M	16	Mandible	Curettage	Recurrence at 6 mo, treated by curettage and cryotherapy; no recurrence (1 y)
Giddings et al[6]	1989	M	10	Mandible	Resection and graft	No recurrence (3 y)
		M	14	Mandible	Resection	No recurrence (1 y)
Present study	1990	M	32	Mandible	Resection	No recurrence (5 mo)

NR — not reported.

***Aneurysmal bone cyst associated with primary bone lesion.**

recurrence rate (38%), including multiple recurrence in several patients. The affected bone was resected in 20 cases (32%), and the recurrence rate among these patients was 25%. External beam irradiation was used to treat 3 patients (5%), in 1 of whom disease recurred. Curettage followed by cryotherapy was used as treatment in 2 cases (3%), and disease did not recur.

Coincidental primary lesions were reported in association with aneurysmal bone cyst 12% of the time. These lesions included fibrous dysplasia (2 cases), cementifying fibroma (2 cases), giant cell reparative granuloma (1 case), fibro-osseous lesion (1 case), and an unspecified lesion (2 cases).

Clinical Development. The lesion typically appears as a firm, painless, and localized swelling, present from 1 week to 3 years. Although gradual expansion of the lesion occasionally perforates the bony cortex, the overlying mucosa remains normal.[52] The mass may be bony and hard or may be firm and rubbery. Crepitation, resulting from the fragile shell of periosteal new bone growth encompassing the lesion,[58] may be detected.

Radiographic Appearance. Aneurysmal bone cyst appears on x-ray films as a unilocular or occasionally multilocular cystic mass with multiple septa, giving it a soap bubble appearance. The radiographic features are characteristic but are not diagnostic.[59]

The thin cortical shell of the lesion is usually well shown by a CT scan, even when not shown on plain x-ray films.[60] Fluid levels also are often seen on CT scans. Magnetic resonance imaging is superior to CT in determining the extent of tumor within the bone marrow.[60] Angiography may show moderate hypervascularization of the lesion with patchy contrast filling of the cystic area and a moderately large arteriovenous shunt.

Radionucleotide Imaging. Radionucleotide imaging studies were reported in 2 aneurysmal bone cysts of the jaw. Features specific to aneurysmal bone cyst that might distinguish it from other lesions[51] could not be found.

Manometric Pressure. Evidence suggests that aneurysmal bone cysts may have higher manometric pressure than other benign cysts. Finding an elevated intracystic pressure may thus facilitate the differential diagnosis. Because elevated intracystic pressure is associated with increased intraoperative blood loss,[58] preoperative planning should include available blood products.

Pathologic Features. A definitive diagnosis of aneurysmal bone cyst can be made only by its microscopic features. The lesion is a pseudocyst composed of blood pools of variable sizes lined by spindle-shaped cells and multinucleated giant cells. The stroma is composed of giant cells, fibroblasts, capillaries, extravasated blood cells, and hemosiderin. The walls of the blood pools do not contain elastic elements or smooth muscle and thus do not mimic blood vessels.[10,23]

Differential Diagnosis. The differential diagnosis of mandibular aneurysmal bone cyst includes giant cell granuloma, juvenile fibromatosis, desmoplastic fibroma, fibrous histiocytoma, fibrous dysplasia, ossifying hematoma, neurofibroma, fibrosarcoma, osteosarcoma, neuroblastoma, and a group of odontogenic lesions including ameloblastic fibroma, odontogenic myxoma, and cementifying fibroma.[6] Exuberant fibrous connective tissue stroma and associated multinucleated giant cells are histologic features also found in giant cell granuloma, hyperparathyroidism, and cherubism. The distinguishing additional feature of aneurysmal bone cyst is the presence of prominent cavernous vascular spaces.[48]

Pathogenesis. The cause of aneurysmal bone cyst remains unclear, although several theories have been suggested. Aneurysmal bone cyst is definitely a nonneoplastic lesion, and no evidence exists to suggest that trauma has any role other than to signal a preexisting lesion.[31]

Lichtenstein[2] proposed that the lesion originates in a circulatory disturbance, which leads to a dilated and congested vascular bed. This engorged vascular bed then causes resorption of spongy bone, erosion of cortical bone, and expansion of the lesion, which is why it is described as "aneurysmal."

Biesecker et al[3] proposed that formation of aneurysmal bone cyst is secondary to a primary benign bone lesion. The primary lesion prompts arteriovenous malformation, thereby creating a secondary reactive bone lesion (known as aneurysmal bone cyst). These investigators support this theory by reporting a series of 66 cases in which a primary bone lesion accompanied an aneurysmal bone cyst in 32%.

Bernier and Bhaskar[10] proposed that aneurysmal bone cyst begins as a focus of intramedullary hemorrhage and that the lesion represents an unusual reparative response to hemorrhage. If a connection is maintained between the hematoma and the damaged blood vessel, aneurysmal bone cyst results. If the connection is obliterated, giant cell reparative granuloma results.

Therapy. Aneurysmal bone cyst is treated by surgical excision, which ranges from enucleation and curettage to conservative resection. Simple curettage for aneurysmal bone cyst is reported to be associated with a high recurrence rate (59%), a result of the difficulty of completely excising such a vascular lesion.[3] Preoperative angiography and embolization of feeding vessels, as well as ligation of the external carotid artery, are done with good success.[20,48]

When enucleation is incomplete, radiotherapy may be effective in eradicating residual disease.[61] Irradiation is also useful as the primary therapy for aneurysmal bone cyst when the lesion is surgically inaccessible.[61] External beam radiation doses ranging from 10 to 20 Gy have been given.[11] After irradiation, the aneurysmal bone cyst involutes and ossifies, resulting in new bone formation. The lesion shrinks little, if at all, and x-ray films show a dense, irregular, sclerotic area.[32] Because of the potential for malignant degeneration of the lesion after treatment, however, radiotherapy is hazardous.[61]

Cryosurgery can be done successfully after curettage of the lesion and is associated with a lower recurrence rate than is curettage alone. Freezing adjacent vasculature extends the surgical boundaries of the curetted excision. This is done by placing the cryoprobe directly into the surgical bed. Use of cryotherapy after curettage of all aneurysmal bone cysts was advocated by El Deeb et al[42] and by Saltzman and Jun.[43]

CONCLUSION

Aneurysmal bone cyst is a benign lesion, found rarely in the jaw, which causes local destruction by expansion and erosion. The lesion develops mainly in young people and affects women slightly more frequently than men. Evidence suggests that it originates from local vascular malformation caused by coincidental primary bone lesions. Although aneurysmal bone cyst is benign, it tends to recur after incomplete resection. The therapeutic challenge is to remove tissue conservatively yet excise affected tissue completely. Thorough curettage followed by cryotherapy of the cyst bed is relatively safe and effective.

The question of whether to pursue immediate or delayed reconstruction is controversial. In this case, immediate reconstruction was not undertaken, because we were not confident that treatment was complete. Subsequent reconstruction has not been recommended because of risk to the facial nerve.

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RHINOPHYMA: A NEW APPROACH TO HEMOSTASIS

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Rhinophyma is a benign tumor of the nose. It possesses both functional and cosmetic implications. The pathophysiology of the disease is reviewed to illustrate the basis for the treatment options. Many different therapeutic modalities have been reported in the literature, each with reasonable success. A new treatment approach to this condition is developed using a combination of the Weck blade and the argon beam coagulator. This modality is found to be relatively simple and less traumatic than all the other techniques used by the senior author.

KEY WORDS — argon beam coagulator, hemostasis, rhinophyma, Weck blade.

INTRODUCTION

Rhinophyma is a form of rosacea involving the nasal skin. It adversely impacts both the appearance and the function of the nose. Rhinophyma was recorded by Greek and Arabic physicians as early as 2000 BC.[1-3] However, Hebra (1845) is credited with the initial description of the malady.[3] This disease is a well-known facial abnormality of older men, and is depicted in Domenico (Bigordi) Ghirlandajo's painting *Old Man With a Child* from the 15th century.[4] Numerous terms have been used to describe the condition, including elephantiasis and potato nose. Incorrectly, many have implied a relationship between alcohol consumption and rhinophyma.

A patient with rhinophyma normally seeks treatment because of the cosmetic deformity, and many treatment modalities, both medical and surgical, have been devised to manage this disease. The medical treatment of rhinophyma is relegated to 1) treating the obvious stimulating factors for rosacea by cleanliness, avoidance of stress, and prevention of infection and 2) treating the complications of rhinophyma by steroids for the prevention of scar formation and antibiotics to prevent secondary infections. The use of isotretinoin (13-*cis*-retinoic acid; Accutane) has been reported to reduce the volume of the sebaceous glands,[5] but has little value in end-stage rhinophyma. Radiotherapy has been proposed for the treatment of acne; however, the use of this modality in the treatment of a benign disease, with its potential of carcinogenesis, cannot be justified. In general, medical therapy for this condition has only limited success.

The relatively unsuccessful experience with medical therapy of this disease leaves surgery as the mainstay in its management. Different surgical modalities have been proposed, including 1) total excision of the abnormal tissue with either flap closure or grafting of the defect and 2) partial excision of the superficial hypertrophic tissue (superficial decortication) allowing the basal skin appendages to reepithelialize. Total excision of the tumor with flap closure or grafting is only applicable when the tumor is small or a skin cancer is present. With extensive rhinophyma, partial excision of the lesion with reepithelialization is the optimum method of management.

There are numerous examples in the literature of the different techniques for decortication of rhinophyma. These include simple scalpel excision,[6] cryosurgery,[7] electrocautery,[8,9] dermabrasion,[6,10] and laser therapy. Use of carbon dioxide (CO_2)[9,11] and argon[12] lasers has been proposed. Various combinations of the above techniques have also been reported.[13-16] In the past few years CO_2 laser excision of this lesion has been the most popular modality and was our choice for most of the past 10 years.

The above-mentioned surgical options are mostly quite successful in the smaller lesions. With larger rhinophymas, the efficacy of the treatment modalities is not as uniform. The senior author (F.J.S.) has tried numerous surgical modalities, with various degrees of success. All were found to have some inherent problems. The complications of excessive removal of hypertrophic sebaceous glands and penetrating too deeply can lead to abnormal scar contracture and subsequent deformity compromising both the cosmetic and functional results. Any one of the above-mentioned methods can lead to this deformity if the depth of excision is not carefully monitored. Recently we devised a surgical method that is rela-

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tively simple and safe and has minimal morbidity while providing excellent hemostasis and cosmetic results. Although our experience with other surgical techniques often yielded good cosmetic results, there were always some unacceptable aspects. The use of the CO2 laser was thought to be an optimum modality except for the operating time involved. Our new method possesses all the advantages of the CO2 laser but is carried out with much more alacrity.

Proponents of CO2 laser excision have described it as precise, efficient, and providing excellent hemostasis. The CO2 laser's ability to seal off blood vessels up to 0.5 mm in diameter[16] is the basis for its hemostatic property. But vessel dilatation is a consistent feature of rhinophyma, and the disease is associated with telangiectasia. For these reasons, the use of the CO2 laser has not been a very good hemostatic modality in managing rhinophyma. Use of the CO2 laser for resection, especially with the use of an operating microscope,[11] involves an operating time of more than 60 minutes, especially if general anesthesia is employed. The method we have devised is a product of our experience treating over 79 rhinophymas. It has the advantage of being simple, with superb hemostasis, while markedly minimizing the operating time required.

PATIENTS

Over the past 18 months, 7 patients with rhinophyma have been treated with this new technique at the Louisiana State University Medical Center, Shreveport, La. The average age of the patients was 66.7; all were men; 4 were white and 3 black (see Figure, A,B). Five patients presented for cosmetic reasons, and 2 for nasal obstruction. Four patients had local anesthesia with intravenous sedation, and 3 underwent general anesthesia. The reasons for general anesthesia were patient request and multiple procedures.

TECHNIQUE

The patient's face is prepared with Betadine solution and then washed with normal saline solution. The face is draped in a sterile fashion with the nose exposed. Xylocaine 0.5% and 1:200,000 epinephrine are used for local anesthesia. A copious injection of anesthetic solution is infiltrated in the subdermal plane. The local anesthesia serves other purposes than anesthetizing the nose and achieving hemostasis by its vasoconstrictive effect. Another function that the local anesthetic solutions serve is to distend the soft tissue tumor from the supporting structures of the nose, thus making dissection more propitious. It also serves the hemostatic function of tamponading the larger local blood vessels. In order to achieve this tamponadic effect, the local anesthetic solution is injected under significant pressure until local tissue pressure prevents any further instillation (see Figure, C). The amount injected is usually in the range of 10 to 15 mL.

The surgical procedure is routinely completed in approximately 10 minutes, following a wait for the vasoconstrictive effects. A Weck blade is used to carve the rhinophyma from cephalic to caudal (see Figure, D). Special care is taken in resecting the tumor from the alae, because there is less predictable depth and there is a possibility of damage to the lateral crus of the lower lateral cartilage. The amount of tissue removed depends on the thickness of the rhinophyma. The goal of the excision is to remove the bulk of the rhinophyma while leaving basal appendages to reepithelialize the nose. The fine contouring of the nose is done also with the Weck blade after the bulk of the tumor has been removed. A rim of normal tissue is left in the alar region to prevent scar contracture, especially around the lateral alar rim.

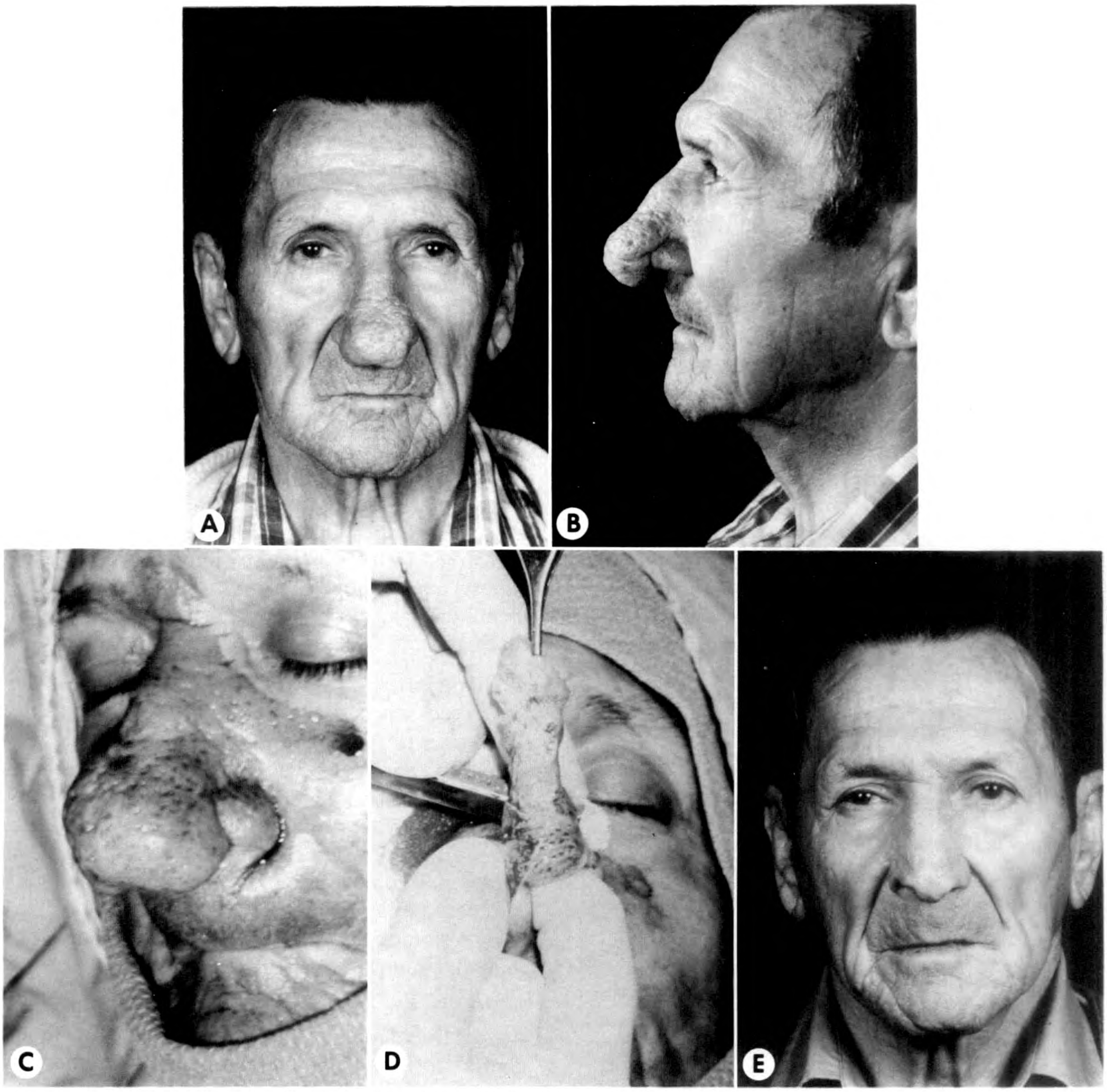
The argon beam coagulator (ABC; Bircher Electromedical Systems, Inc, Englewood, Colo) sweeps and coagulates the entire wound bed. It is set at 60 W, with exposure time generally less than 3 seconds. Any area that has scant skin appendage is only lightly coagulated with the ABC. In our experience, only 1 pass of the ABC is adequate for hemostasis.

Following the procedure, copious amounts of vitamin A and D ointment are applied as the only dressing. The procedure is carried out as day surgery. Instructions on discharge include cleansing of the wound with hydrogen peroxide on a twice a day basis and regular application of A and D ointment to keep the wound moist to facilitate reepithelialization. Intraoperative or perioperative antibiotics are not used.

RESULTS

There were no intraoperative complications, and the average blood loss for the procedure was approximately 5 mL. An eschar forms, usually by 24 hours. By the 5th postoperative day, epithelialization is evident, and it is usually completed in 3 to 4 weeks.

The cosmetic results are graded as poor, good, or excellent as per Clark and Hanke.[8] Three of our patients achieved excellent results, 4 had good results, and none had poor. All 3 of the patients with excellent results were white. The follow-up period averaged 4 to 18 months. Experience with 79 cases indicates little change in the results after 4 months. Minor complications postoperatively involved small hypertrophic scars in the superior edge of the exci-



Seventy-year-old white male with severe rhinophyma. A) Frontal view. B) Lateral view. C) Hydrodissection of rhinophymatous tissue. D) Weck blade dissection of rhinophyma. E) Patient 6 months postoperatively.

sion or dorsum of the nose and also hypopigmentation on the reepithelialized skin. Hypopigmentation occurred in all 3 of our black patients, and 2 of the black patients had hypertrophic scars at the superior part of the excision. Our 1 white patient who achieved only a good result had nasal valvular problems for which he had had a previous nasal procedure. The 2 patients with hypertrophic scars were treated with Kenalog injections with satisfactory results.

All the patients achieved marked airway improvement almost immediately postoperatively, and none required repeat excision of the rhinophyma (see Figure, E). All the pathologic specimens were consistent with rhinophyma, with no carcinoma detected.

DISCUSSION

The treatment of rhinophyma has been primarily surgical, and a review of the literature reveals a large number of surgical techniques available. Recently, the most popular method of treatment has been the use of the CO_2 laser, either as a sole modality[9,11] or for contouring of the tumor following scalpel removal.[13] We treated 34 patients with the CO_2 laser over an 8-year period prior to abandoning this treatment for the alacrity and simplicity of our new technique. Our method of treatment, using the Weck blade and the ABC, appears to be a simpler and more precise method of removing this cosmetically disfiguring tumor.

The advantages of the laser have been well documented.[11] With regard to our new method of removing rhinophyma, a few interesting points can be discussed. It has been recommended that an operating microscope be used in conjunction with the CO2 laser to improve the precision of excision,[11] which will require expertise acquired from practice. The use of the Weck blade will give equally good nasal contouring without the need of the operating microscope if the tumor is filleted incrementally and the procedure is done in a conservative fashion. One may find that the use of 2.5× magnification loupes is beneficial. From our experience, the CO2 laser in the defocus mode has not been a good hemostatic instrument for vessels larger than 0.5 mm, as has been reported in the literature by Wheeland et al.[17] A review of the pathologic process in rhinophyma will demonstrate that there is a component of vascular dilatation; therefore, the pathologic findings confirm our clinical observation that the CO2 laser in a defocus mode is not adequate for cautery purposes. The use of the ABC as a hemostatic instrument has proven to be beneficial in many head and neck procedures with much larger vessels, ie, neck dissection.[17,18] The ABC in our experience is simpler to use and more readily controls bleeding once nasal contouring is achieved; usually 1 pass of the instrument is required to secure hemostasis. The amount of bleeding during the nasal contouring portions of the procedure is significantly decreased by our injection technique of applying as much local anesthetic agent as the tissue can accommodate in order to achieve a tamponading effect, plus the use of epinephrine for its vasoconstrictive properties.

The ABC uses ionized argon gas to conduct current to tissue. In the target mode, the tip of the nozzle is more than 1 cm away from the tissue surface, where a stream of argon gas is blown onto the tissue, thus blowing away any blood and allowing coagulation of dry vessels. In the active mode, the nozzle is less than 1 cm away from tissue, and radio frequency energy is conducted through the gas stream via the arcing process to allow coagulation to occur. This process can coagulate vessels up to 2 to 3 mm in diameter and larger.[17] This allows control of vessels up to 10 times the size of those coagulated with the defocused CO2 laser. The arcing process distributes the radio frequency energy more evenly onto the tissue in comparison to conventional coagulation. The argon gas also displaces oxygen and nitrogen from the tissue surface, decreasing the amount of smoke produced. By clearing blood from the wound surface, it prevents the formation of a nonadherent eschar.[19]

The limited depth of tissue destruction by the ABC has been demonstrated by Teimourian et al.[18] With the ABC setting below 80 W and exposure time less than 3 seconds, the depth of tissue injury is less than 0.5 mm, and usually in the range of 0.2 to 0.4 mm. This is much less than the depth of destruction caused by an electrocautery, which at a 40- to 60-W power setting causes 0.66 to 1 mm of tissue destruction.

No untoward effect will result if the initial soft tissue contouring of the nose is carried out in a conservative fashion, which implies sparing the perichondrium or periosteum and leaving enough of the basal skin appendages to ensure regeneration. The operating microscope is not helpful and is actually awkward in this procedure. Employing magnification loupes is also not necessary, but may be helpful in ensuring a precise dissection in the nasal contouring aspect of the procedure.

The average operating time for this technique is about 10 minutes. In our institution the procedure is performed by the staff and by junior residents under supervision without variation in the outcome. This technique has greatly simplified the treatment of this disfiguring disease.

All our procedures were done under local anesthesia, except where other procedures were done at the same time or per patient request. All were done as outpatient surgical procedures, and there were no postoperative complications. Copious amounts of A and D ointment are employed postoperatively. Antibiotic ointment is eschewed, as it adds nothing but an occasional atopic reaction. The patients are instructed to clean the wound with hydrogen peroxide twice daily to remove crusting that can impede the reepithelialization process.

We noticed that all the black patients developed hypopigmentation postoperatively, usually in the central portion of the reepithelializing wound. It is quite unsightly initially, and it is important to inform these patients preoperatively. The hypopigmentation is time-dependent and resolves in about 6 months. This is a natural healing process and is observed in healing abrasions in all black patients.

Two black patients and 1 white patient developed minor scarring problems. The white patient had a small scar contracture in the alar region, where he had had previous nasal valvular surgery. He required surgical correction for this contracture. The 2 black patients developed minor hypertrophy of the scar in the superior portion of the excision margin. Both were injected with local steroid and both scars have softened with time and decreased in size. The hypertrophic scar probably is a natural response of these dark-skinned individuals to the healing process. One of the black patients had preoperative keloid formation in another area. As long as caution is used, this technique is not contraindicated in black patients with keloids.

CONCLUSIONS

The ABC technique that we have evolved has proven to be advantageous in the management of rhinophyma. The technique is divided into 2 parts: 1) use of a Weck blade for contouring the nasal structures after adequate local anesthesia has been injected into the soft tissue to form a tissue plane and give adequate tamponading of the local vessels and 2) the use of the ABC, which in our experience yields optimum hemostasis without traumatizing underlying tissues.

Over the past 20 years, the senior author has managed over 79 rhinophyma patients. The present technique has been found to be the most simple to perform if care is taken during the procedure. Conservation of normal uninvolved tissue, especially in the alar rim, yields an excellent result with good hemostasis and few complications. Black patients require special consideration and should be warned about the potential for hypopigmentation and hypertrophic scars. Unlike other techniques, use of the ABC for this procedure requires no special training for the general otolaryngologist–head and neck surgeon.

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LOCATION OF THE PREEPIGLOTTIC SPACE AND ITS RELATIONSHIP TO THE PARAGLOTTIC SPACE

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An investigation was carried out to determine the location of the preepiglottic space (PES) and its relationship to the paraglottic space (PGS). Excised human adult larynges served as materials for this study. The distribution of the PES of the larynx was determined histologically in 3 whole organ serial sections: sagittal, horizontal, and coronal. The results are summarized as follows. 1) The PES exists not only anterior, but also posterolateral and inferolateral to the epiglottis. 2) Its posterior end is located in the vicinity of the anteroposterior midpoint of the thyroid lamina. 3) The PES is adjacent to the PGS posteroinferiorly and is separated by fibrous tissue (the thyroglottic ligament). Posterosuperiorly, the 2 spaces are not clearly delineated from each other.

KEY WORDS — anatomy of larynx, histology of larynx, paraglottic space, preepiglottic space.

INTRODUCTION

Since the first description by Boyer,[1,2] several authors[3-6] have investigated the preepiglottic space (PES), but a clear indication of its exact location and shape, especially its posteroinferior extension, has not been given. Furthermore, there has been no agreement on the border between the PES and the paraglottic space (PGS). Distribution of these spaces is important in following the spread of carcinoma in the larynx. In addition, the PES is related to the 1987 UICC classification of laryngeal cancer.[7] The purpose of this study is to more clearly define the posteroinferior extension of the PES and the border between the PES and the PGS.

MATERIALS AND METHODS

The material was 30 human adult larynges. Twenty normal larynges were obtained from autopsy cases, and 10 larynges with laryngeal or hypopharyngeal carcinoma were obtained from surgical specimens. Of the 20 normal larynges, 9 were from men with ages ranging from 44 to 75, and 11 were from women with ages ranging from 37 to 81. Of the 10 larynges with carcinoma, 5 had supraglottic carcinoma and 5 had pyriform sinus carcinoma.

The whole organ serial section technique was employed. The specimens were fixed in 10% formalin, decalcified in 5% hydrochloric acid, dehydrated in graded concentrations of ethanol, and embedded in paraffin. Horizontal, coronal, and sagittal serial sections were made. Horizontal serial sections were made parallel to the membranous portion of the vocal folds. Coronal serial sections were made vertical to the membranous portion of the vocal folds. Among 20 normal laryngeal specimens, horizontal serial sections were made from 8, coronal serial sections from 6, and sagittal serial sections from 6 larynges.

Hematoxylin-eosin and elastica–van Gieson stains were employed for each section, and then microscopic observation was performed. Elastica–van Gieson staining facilitated observations of thin fibrous tissue.

Three-dimensional reconstruction of the PES was obtained by means of computer graphic techniques on a personal computer (NEC PC-9801RX) using

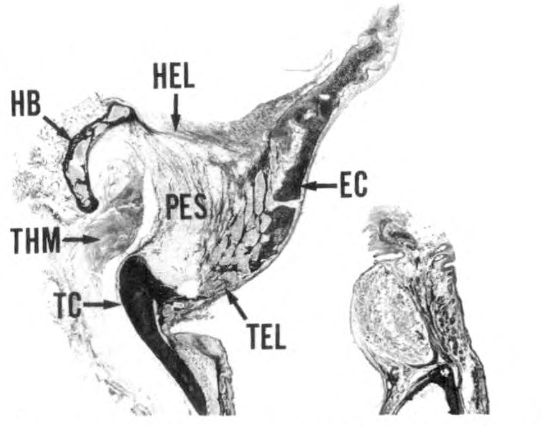

Fig 1. Midsagittal section of larynx (elastica–van Gieson stain [EVG]). PES — preepiglottic space, HEL — hyoepiglottic ligament, HB — hyoid bone, THM — thyrohyoid membrane, TC — thyroid cartilage, TEL — thyroepiglottic ligament, EC — epiglottic cartilage.

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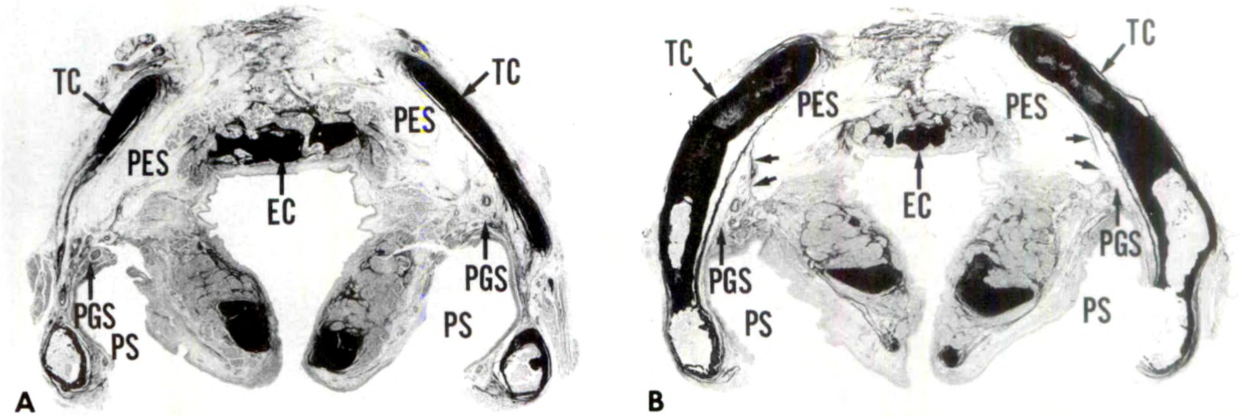


Fig 2. Horizontal sections (EVG). PGS — paraglottic space, PS — pyriform sinus. Other abbreviations as in Fig 1. A) Near upper edge of thyroid lamina. B) At upper portion of thyroid cartilage. Short arrows — thin fibrous tissue delineating PES from PGS.

COSMO ZONE software (Nikon).

RESULTS

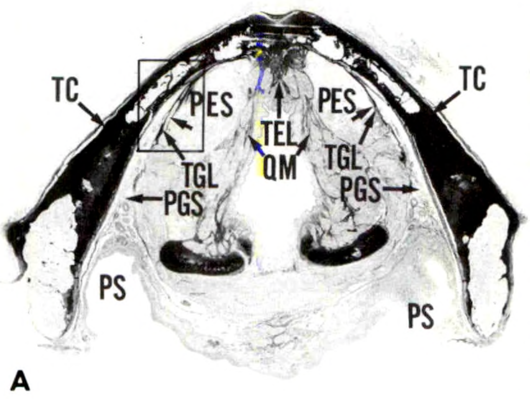
Midsagittal Section. Figure 1 shows a midsagittal section of the larynx. The PES is a loose areolar area and mainly composed of adipose tissue and loose elastic and collagenous fibers. The PES is surrounded by the hyoepiglottic ligament superiorly, by the thyrohyoid membrane and thyroid cartilage anteriorly, and by the thyroepiglottic ligament and epiglottic cartilage posteroinferiorly.

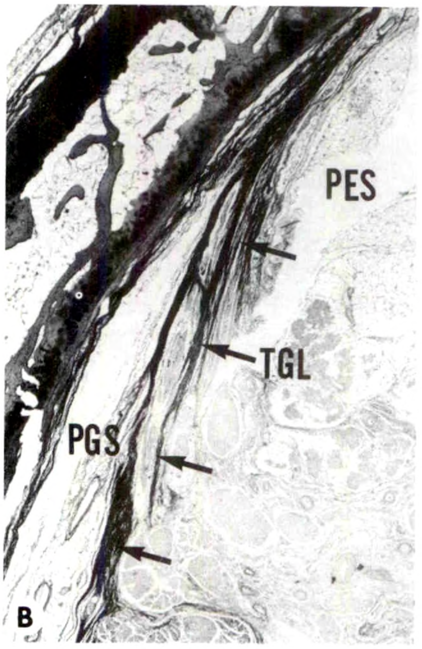
Horizontal Sections. Figure 2A shows a horizontal section near the upper edge of the thyroid lamina. The PES is located anterior, lateral, and posterolateral to the epiglottic cartilage. The posterior end of this space is near the anteroposterior midpoint of the thyroid lamina. Condensation of fibrous tissue is observed in the midline of the PES. The upper portion of the PGS is situated anterior to the pyriform sinus. It is adjacent to the PES, and the 2 spaces are not clearly delineated from each other.

Figure 2B shows a horizontal section at the upper portion of the thyroid cartilage. The PES extends not only anterior but also posterolateral to the epiglottic cartilage. The posterior projection of this space is located in the vicinity of the anteroposterior midpoint of the thyroid lamina. Condensation of fibrous tissue is found in the midline of the PES. The upper portion of the PGS is observed anterior to the pyriform sinus. The PES and PGS are clearly delineated from each other by thin fibrous tissue (short arrows in Fig 2B).

Figure 3A shows a horizontal section at the ventricular fold. The inferolateral portion of the PES is placed lateral and posterolateral to the thyroepiglottic liga-

Fig 3. Horizontal section (EVG). TGL — thyroglottic ligament, QM — quadrangular membrane. Other abbreviations as in Figs 1 and 2. A) At ventricular fold. B) Higher magnification of border between PES and PGS (box in A).





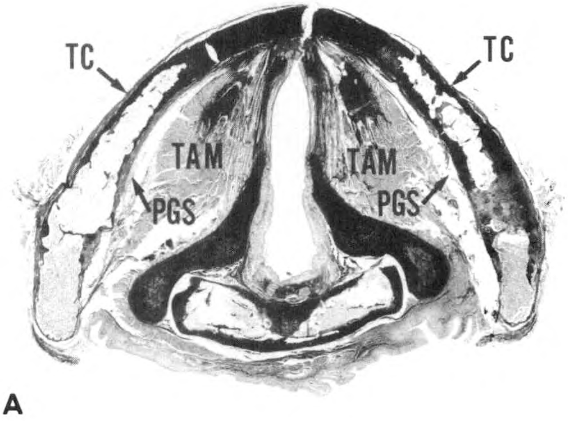
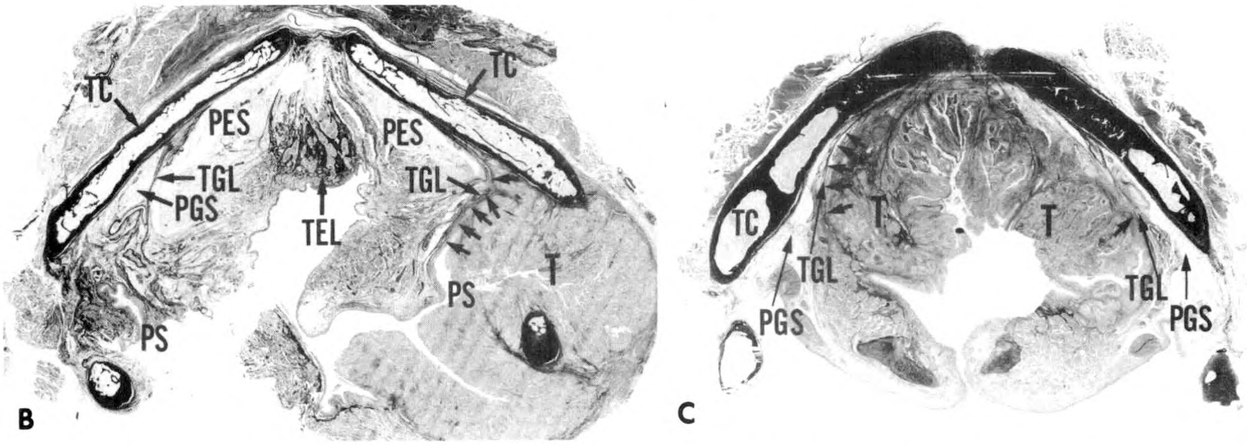


Fig 4. Horizontal sections (EVG). TAM — thyroarytenoid muscle, T — tumor. Other abbreviations as in Figs 1-3. A) At vocal fold. B) At upper portion of thyroid cartilage of larynx with pyriform sinus hypopharyngeal carcinoma. Fibrous tissue blocks tumor invasion (short arrows). C) At ventricular fold of larynx with supraglottic laryngeal carcinoma. Thyroglottic ligament blocks tumor invasion (short arrows).



ment. This space extends not only anterior but also inferolateral to the thyroepiglottic ligament. The PGS exists medial to the thyroid lamina. The PES and PGS are bordered by a thick fibrous structure (arrows in Fig 3B) that has been called the thyroglottic ligament by Tucker and Smith.[3]

Figure 4A shows a horizontal section at the vocal fold level. The PES is no longer observed at this level. The PGS is placed medial to the thyroid lamina along its entire length.

Figure 4B shows a horizontal section at the upper portion of the thyroid cartilage of a larynx with hypopharyngeal carcinoma. The tumor is mainly located at the pyriform sinus and has invaded the upper portion of the PGS. Fibrous tissue blocks the tumor invasion and the PES is intact. This finding indicates that the PES and PGS are separate spaces.

Figure 4C shows a horizontal section at the ventricular fold of a larynx with supraglottic laryngeal carcinoma. The PES is filled with tumor. Fibrous tissue, the so-called thyroglottic ligament, blocks the tumor invasion, and the PGS is intact. This finding supports the view that the PES and PGS represent separate spaces.

Coronal Sections. Figure 5A,B shows the anteroposterior midpoint of the vocal fold. The PES is located not only superior but also inferolateral to the epiglottic cartilage. Condensation of fibrous tissue is observed in the midline of the PES. The PGS is situated medial to the lower two thirds of the thyroid lamina. The PES and PGS are clearly bordered by the so-called thyroglottic ligament (arrows in Fig 5A,B).

Figure 5C shows the coronal section at the anteroposterior midpoint of the vocal fold of a larynx with supraglottic laryngeal carcinoma. The PES is filled with tumor. Fibrous tissue, the so-called thyroglottic ligament, blocks the tumor invasion and the PGS is intact; these findings indicate that the PES and PGS represent separate spaces.

Three-dimensional Reconstruction. Figure 6A shows the superolateral view and Fig 6B shows the anterosuperior view of the larynx. The PES exists around the epiglottis, and extends not only anterior, but also posterolateral and inferolateral to the epiglottis. Its posterior end is in the vicinity of the anteroposterior midpoint of the thyroid lamina. The PES is adjacent to the PGS posteroinferiorly, and they are separated from each other by fibrous tissue (arrows in Fig 6).

DISCUSSION

A space is defined as any demarcated portion of the

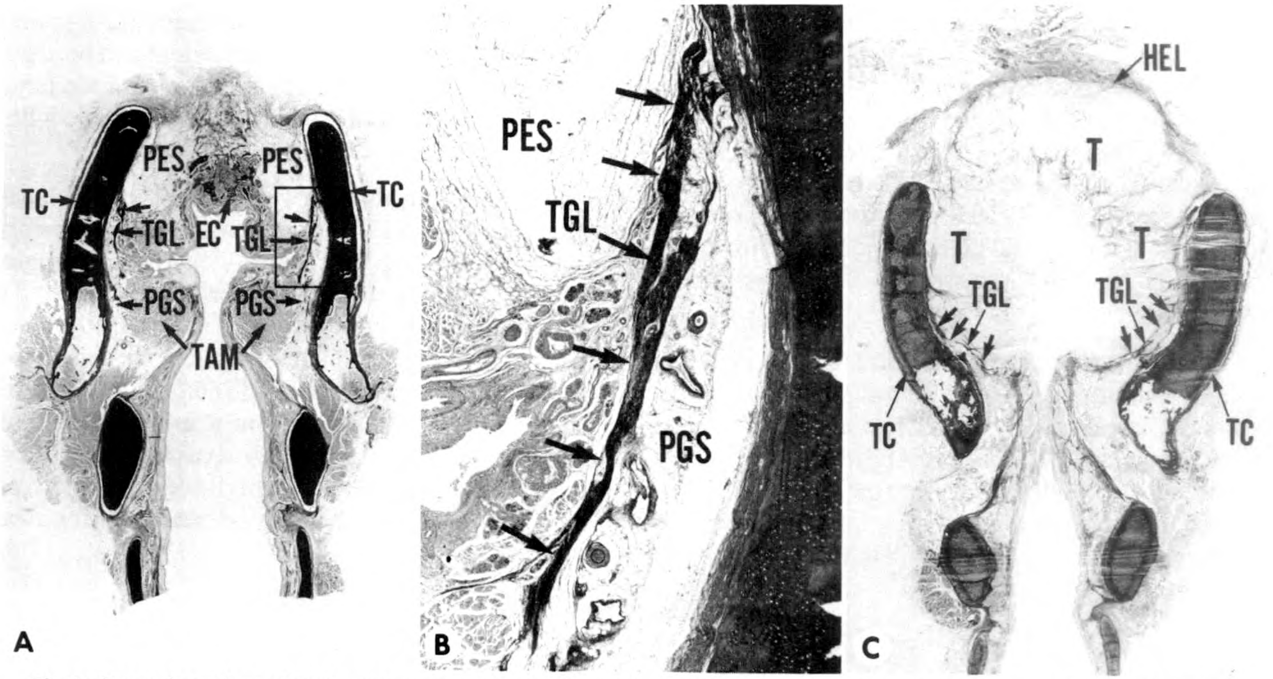


Fig 5. Coronal sections (EVG). Abbreviations as in Figs 1-4. A,B) At anteroposterior midpoint of vocal fold. B) Higher magnification of border between PES and PGS (box in A). Thyroglottic ligament (arrows) is composed of fibrous tissue and runs from thyroid cartilage to thyroarytenoid muscle. C) At anteroposterior midpoint of vocal fold of larynx with supraglottic laryngeal carcinoma. Thyroglottic ligament blocks tumor invasion (short arrows).

body, which can be an area of the surface, a segment of tissues, or a cavity.[8] The chief laryngeal spaces are the PES and PGS. Both of these spaces are very important clinically, but are commonly used terms and are not included among standard anatomic terms (Nomina Anatomica). There is confusion in the literature regarding the definition of these spaces, and there is no agreement on their distribution. We investigated these spaces using whole organ serial section techniques and computer-aided 3-dimensional reconstruction.

The PES of the larynx is a loose areolar area composed of loose elastic and collagenous fibers and adipose tissue. Since Boyer[1,2] first described the PES as the prelaryngeal bursa anterior to the thyrohyoid membrane, several authors have defined its extension. As was described regarding findings at the midsagittal plane, the PES is surrounded by the hyoepiglottic ligament superiorly, by the thyrohyoid membrane and thyroid cartilage anteriorly, and by the thyroepiglottic ligament and epiglottic cartilage posteroinferiorly.[4] Clerf[4] noted that as the lower part of the epiglottis narrows, the remainder of the posterior boundary of the PES is formed by an elastic membrane. Tucker and Smith[3] described this space as the loose areolar area in front of and alongside the epiglottis. Norris et al[5] defined it as the midline space anterior to the epiglottis, bounded superiorly by the hyoepiglottic ligament. Its lateral limits are those

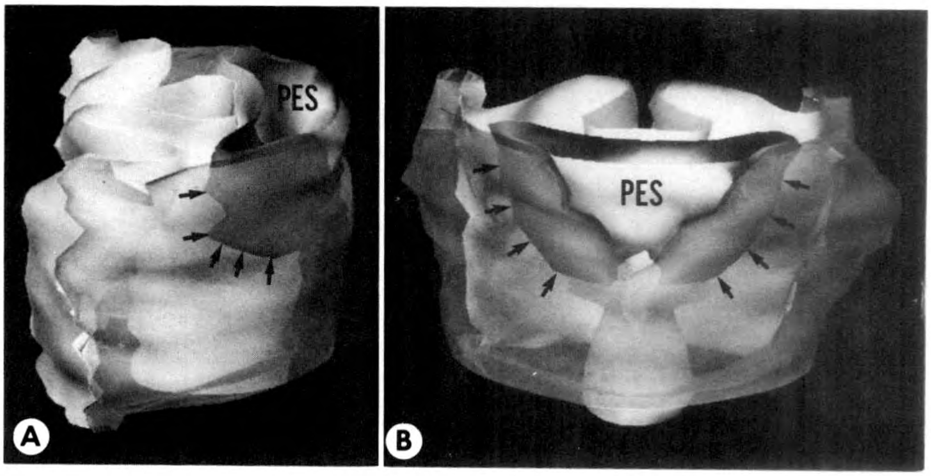


Fig 6. Reconstructed images of preepiglottic space (PES). Arrows — border between PES and paraglottic space. A) Viewed from superolateral. B) Viewed from anterosuperior.

fibers that travel more vertically from the hyoid to the lateral edges of the epiglottis. All these authors noted that the PES exists not only anterior, but also lateral, to the epiglottis. Whereas there is no general agreement on the posterior and inferior limits of this space, our detailed investigation revealed that the posterior end of the PES is located near the anteroposterior midpoint of the thyroid lamina, and its inferior end is bounded by fibrous tissue (the so-called thyroglottic ligament).

Previous reports have indicated that the PES and PGS are continuous.[3,6] Our investigation with elastica–van Gieson stain, however, reveals that the PES is adjacent to the PGS posteroinferiorly and is separated from it by fibrous tissue (the so-called thyroglottic ligament), whereas the 2 spaces are not clearly delineated from each other posterosuperiorly. The fibrous tissue, the so-called thyroglottic ligament, blocks the tumor invasion. This extent and border of the PES suggests that an invasive supraglottic laryngeal carcinoma in this space can be resectable with a supraglottic horizontal laryngectomy.

From the physiologic point of view, previously mentioned, the PES bends the epiglottis posteriorly during swallowing. In laryngeal closure the preepiglottic body (PES) and tubercle are applied to the top of adducted vestibular folds and are pressed against them by approximation of the hyoid bone and thyroid cartilage.[9] The distribution of the PES in this study suggests that it plays this role more actively. In addition, this space appears to act as a cushion whose purpose is to protect the epiglottic cartilage from mechanical damage that may be caused during swallowing.

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4TH INTERNATIONAL ACADEMIC CONFERENCE IMMUNOBIOLOGY IN OTOLOGY, RHINOLOGY AND LARYNGOLOGY

The 4th international academic conference Immunobiology in Otology, Rhinology and Laryngology will be held in Oita, Japan, April 4-7, 1994. For further information contact Goro Mogi, MD, Dept of Otolaryngology, Oita Medical University, Hasama-machi, Oita 879-55, Japan; telephone 81-975-49-4411 ext 2912 or 2913; fax 81-975-49-0762.

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EXPERIMENTAL TRACHEAL TUBE CREATED WITH VASCULARIZED FASCIA

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An experimental fascial transferable bed was developed in the rabbit model. This tissue is reliable in bringing a viable mucosal graft inside the larynx. A vascular connective tissue sheet with full-thickness mucosa and autogenous cartilage for external support are needed. In this study a tracheal tube was preformed to study the use of autogenous cartilage as support for a circumferential lumen.

KEY WORDS — fascia, trachea, tube, vascular system.

INTRODUCTION

An experimental model was developed with a vascularized transferable bed. This brings a mucosal lining on a vascular bed inside the lumen of a repaired upper airway wall.[1,2] The vascular bed consists of the axial perfused lateral thoracic fascia in the rabbit. It is the experimental counterpart of the free human fascial flaps (thoracodorsal, radial, temporal). Autogenous cartilage was chosen for external support, as it preserves its full viability within a well-vascularized fascial bed. The value of the mucosal graft inside the lumen of a laryngeal defect was studied in a previous experiment (Delaere et al, unpublished observations). The use of autogenous cartilage to support a defect and to maintain a circular tracheal lumen is evaluated. There are few indications for a circumferential tracheal reconstruction. Resection and primary anastomosis is the reparative method of choice when the involved segment is less than 5 cm.[3-5]

The reason for this experiment was not to present a method for circumferential tracheal reconstruction. We rather wanted to evaluate the supporting value of autogenous cartilage when used for upper airway wall reconstruction with vascularized fascia as the basic material and oral mucosa as the internal lining. We believe that this problem could be evaluated best with the construction of a circumferential tracheal segment.

A successful reconstruction of a neotracheal segment requires that the following criteria be met.

1. The tracheal inner surface must be lined with some sort of epithelium.
2. A stable and flexible structural framework should be provided.
3. An adequate vascularization to keep the reconstructing components viable should be provided.

These requirements are fulfilled when using vascularized fascia, oral mucosa, and autogenous cartilage grafts.

A cartilaginous and membranous tracheal tube was created by suturing a mucosal graft, applied in the middle of the lateral thoracic fascia, over a silicone tube (Fig 1). Four longitudinal cartilage strips were constructed over the fascia, bearing the mucosal graft, as support of the lumen. The cartilage strips were circumferentially embedded in vascularized tissue by rotating the distal end of the fascia over the reconstruction (Fig 2). The effect of rotation of the vascularized bed on the blood supply had been studied previously. No deleterious effect on the distal vascularization was found after rotating the fascia over 360°.[1]

MATERIAL AND METHODS

Twenty New Zealand White rabbits weighing 2,800 g were used in this investigation. The animals were divided into 3 groups. The first group (control group) consisted of 10 rabbits in which no cartilaginous support was inserted into the tube reconstruction. They were followed up for 8 weeks after operation. The second group consisted of 5 rabbits with cartilaginous support, followed up for 4 weeks. The third group consisted of 5 rabbits with cartilaginous support, followed up for 8 weeks.

Operative Technique. The rabbits were placed in the supine position. Anesthesia was induced by intramuscular administration of Hypnorm and maintained with a halothane-oxygen mixture through a mask. After shaving and scrubbing of the lateral thoracic area with Betadine and alcohol, the left lateral thoracic skin was incised and dissected from the under-

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From the Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital St Rafaël, Leuven, Belgium.

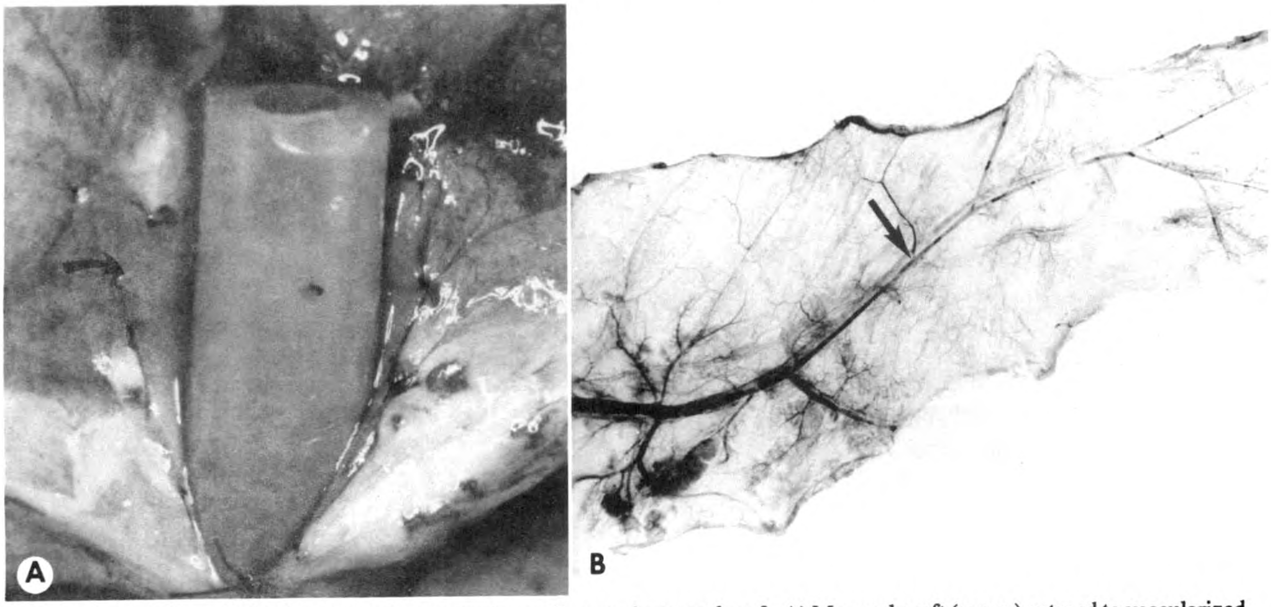
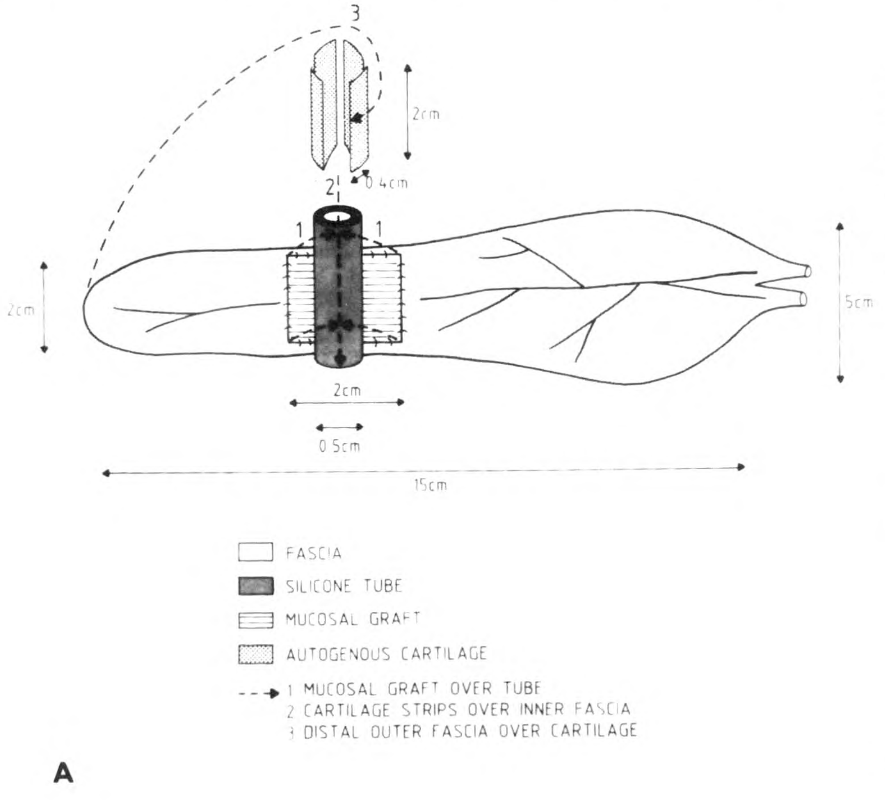


Fig 1. Lateral thoracic fascia as vascular carrier for cartilage and mucosal graft. A) Mucosal graft (arrow) sutured to vascularized fascia is circumferentially brought around silicone tube. B) Vascular pattern of lateral thoracic fascia flap after injection of India ink. Axial perfusion through dorsal branch of lateral thoracic artery and vein (arrow).

lying fascia. The fascia with its axial pattern of vessels was elevated from the muscles of the lateral chest wall and pedicled on the lateral thoracic artery and vein.

In this way, a fascial flap was harvested with a length of 15 cm and a width of 5 cm. Two full-thickness oral mucosal grafts of 1 × 2 cm were obtained from the left and right buccal areas. The created oral defect was closed primarily with 4-0 catgut.

The 2 oral mucosal grafts were placed one beside the other on the middle part of the fascial flap and sutured to the vascular bed with 9-0 nylon. The mucosal graft with the underlying fascia was wrapped around a silicone rod (6-0 nylon) with a diameter of 0.5 cm to form a mucosal-lined tube with a length of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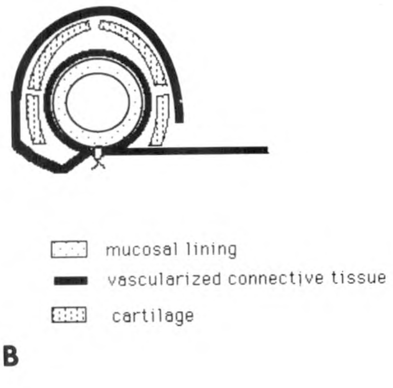
AUTOGENOUS CARTILAGE
1 MUCOSAL GRAFT OVER TUBE
2 CARTILAGE STRIPS OVER INNER FASCIA
3 DISTAL OUTER FASCIA OVER CARTILAGE
A

Fig 2. Principle of tracheal tube creation. A) Different steps in creating tracheal tube. 1—Mucosal graft circumferentially brought around silicone tube, 2 — four cartilage strips applied over fascia bearing mucosal graft, 3 — distal end of fascia sutured over cartilage strips. B) Cross section of neotrachea. Mucosal-lined lumen with cartilage strips circumferentially enclosed in vascular bed.



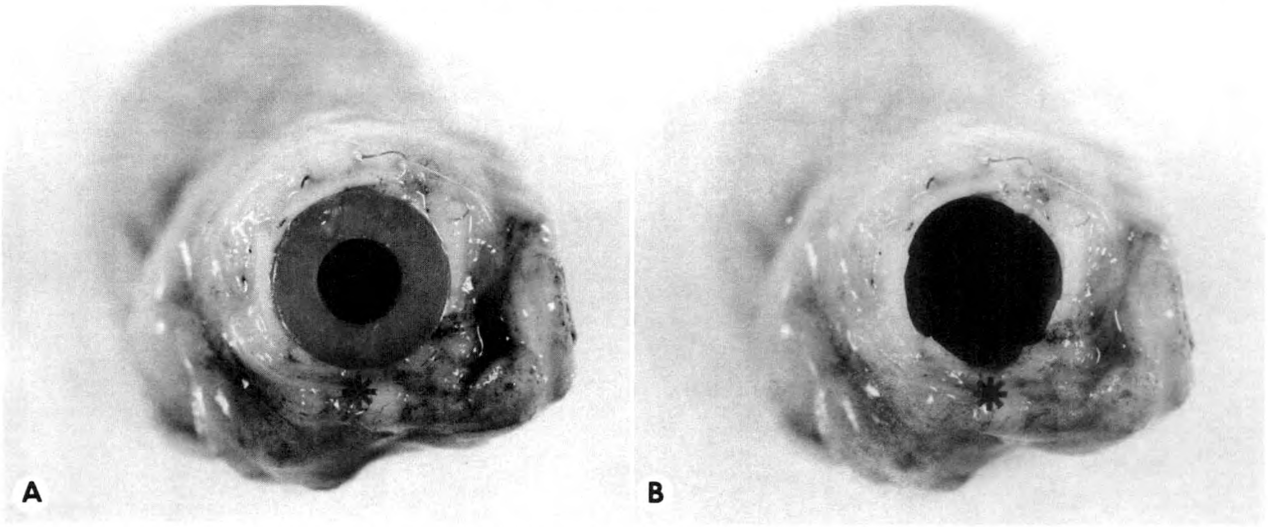


Fig 3. Photographs of reconstructed lumen. A) Silicone tube in place. B) Lumen after removal of silicone tube after 4 weeks of follow-up. Loss of lumen diameter is most pronounced in membranous region (asterisk).

2 cm (Fig 1).

One 10 × 20-mm section of cartilage was removed from each ear root with the perichondrium intact. The perichondrium was included on the cartilage graft to ensure its mechanical strength and to enhance its healing to surrounding tissues. Four cartilage strips of 4 × 20 mm were obtained from the 2 pieces and placed over the inner fascia with 6-0 nylon to create a cartilaginous framework. The dorsal membranous part was formed by the fascia entering and leaving the created tube. Finally, the distal end of the fascia was brought over the cartilage framework, which was enclosed by inner and outer vascular layers (Fig 2). The lateral thoracic skin was closed over the neotrachea with 3-0 Vicryl. The treatment and care of the rabbits followed the rules of the American Physiological Society.

The operative technique was identical in the 2 groups, except for the cartilaginous support, which was not introduced between the 2 fascial layers in the first group.

The lateral thoracic area was reopened after the follow-up period. The subscapular trunk was dissected free and injected with India ink 10% gelatin to visualize the blood vessels within the inner and outer vascular beds. After injection, the vascular pedicle was cut and the neotrachea was harvested with the silicone tube still in place. Black-and-white photographs were taken from the neotracheal specimens with and without the tube and were developed at 5× magnification.

Representative samples of each group were wax-embedded, transverse-sectioned, and stained with hematoxylin and eosin. The black-and-white photographs were then used to trace out 2 perimeters: the outer diameter of the silicone tube and the inner mucosal lining of the preserved lumen after the removal of the silicone rod (Fig 3). The cross-sectional area was computed on an image analysis program (CANVAS 3.0).

RESULTS

The shape of the lumen of the tracheal cross-sectional area without the silicone tube in place was subtracted from the cross-sectional area with the tube.

The mean losses of tracheal area measurements were 385.22 mm^2 (SD 24.9) for group 1 (without cartilaginous support), 85.96 mm^2 (SD 33.3) after 4 weeks' follow-up (group 2), and 59.1 mm^2 (SD 15.1)

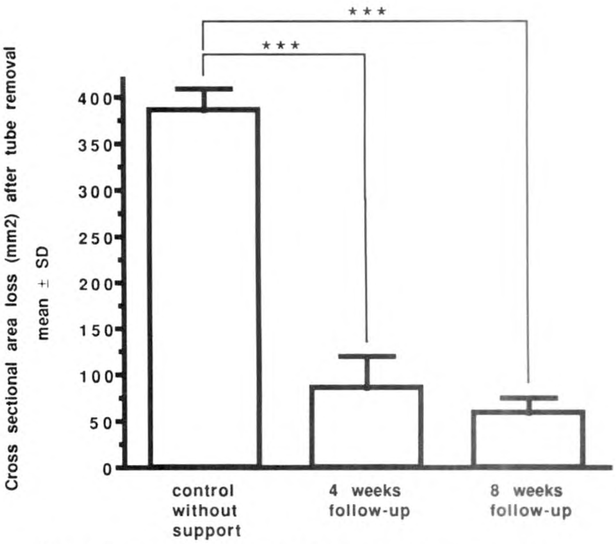


Fig 4. Comparison of tracheal lumen area measurements. There is 79% lumen preservation after 4 weeks, and 86.6% after 8 weeks versus 10.7% for controls. Triple asterisks—difference from control significant at p = .0001.

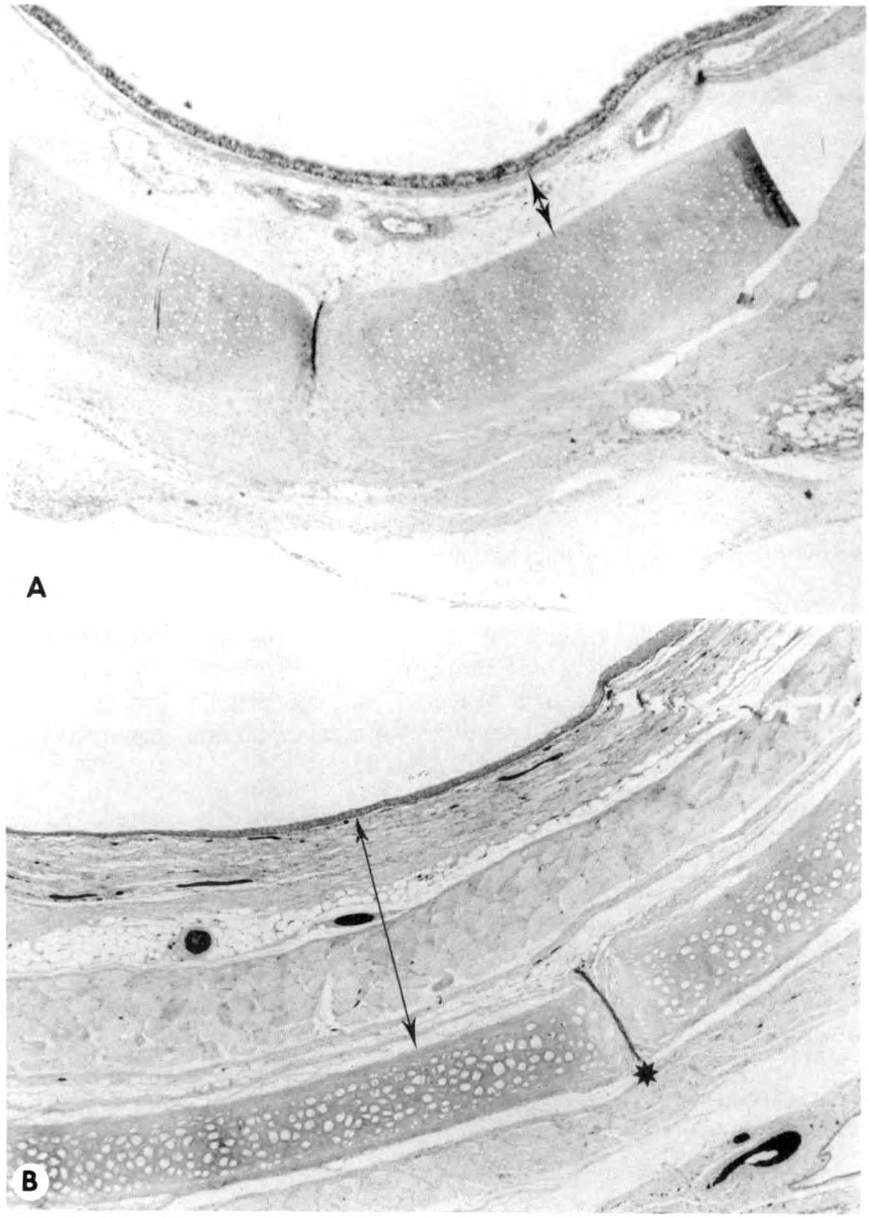


Fig 5. Photomicrographs of normal tracheal wall in comparison with reconstructed tracheal wall (H & E, original ×20). A) Cross section of normal tracheal wall. Arrows — thickness of submucosal tissue. B) Cross section of reconstructed tracheal wall. Arrows — thickness of submucosal tissue, asterisk — formation of fibroconnective tissue between 2 adjacent cartilage strips with formation of pseudoarthrosis.

for the group followed up 8 weeks after operation (group 3; Fig 4).

The histologic appearance of the reconstructed tracheal wall can be evaluated best in comparison with the normal tracheal wall (Fig 5). The nonkeratinized stratified epithelium is visible on the internal layer of the fascial flap. The inner fascial layer with the India ink–injected blood vessels and some muscle cells underneath the fascia is only 1 mm thick. It is, however, still 2.5 times thicker than the submucous layer of the normal trachea. The cartilaginous component is seen between the inner and outer fascial layers. The cartilage viability can be identified by the presence of central or eccentric nuclei containing chromatin. Different areas of new cartilage formation by appositional growth can be observed. The new cartilage can be distinguished by the smaller, more densely packed cells with less accompanying pericellular matrix.

The gap between the cartilage strips is filled with fibroconnective tissue that holds the strips in place (Fig 5B). In some places newly formed cartilage bridges are found. This cartilaginous connection between the 2 cartilage strips is established in 5% of the intervening cartilage spaces after 4 weeks and in 10% after 8 weeks (Fig 6).

DISCUSSION

Circumferential tracheal reconstruction is rarely called for in clinical practice. In most patients, primary anastomosis after resection of up to 5 cm of the trachea is the method of choice. Preforming of

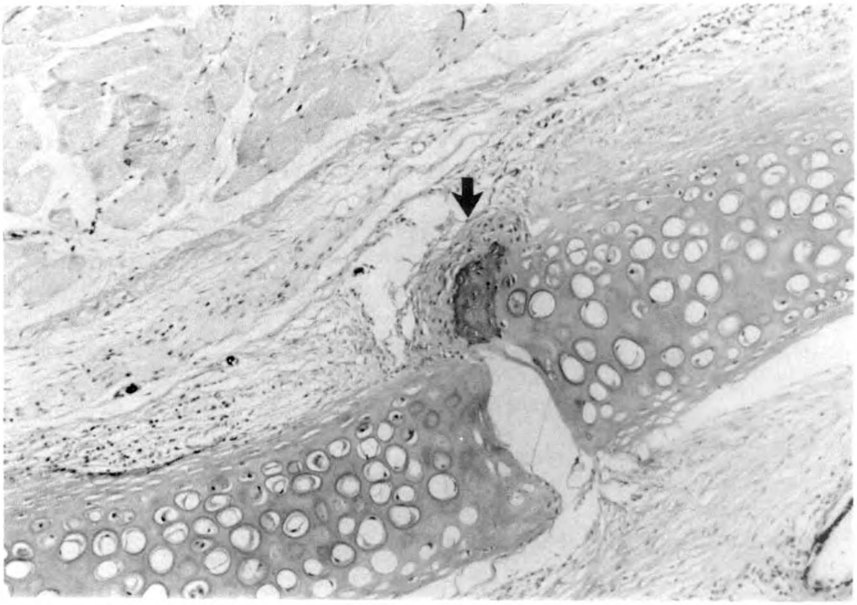


Fig 6. Photomicrograph of gap between 2 adjacent cartilage strips. In some places, cartilaginous bridge is visible (arrow; H & E, original ×40).

neotracheal segments is, however, possible. On the surface it seems simple to replace a tube intended primarily for air passage. The difficulties encountered with neotracheal segments become clear in reviewing the literature. Reconstruction of a tracheal defect has been tried with prosthetic materials such as silicone rubber,[5] porous mesh tubes,[6] and others. The problem with all synthetic materials is the absence of an epithelialized surface, granulation tissue formation at the suture lines, and subsequent infection and extrusion. A cartilage tube can be formed experimentally, taking advantage of the neochondrogenetic effect of perichondrium.[7] Again, the mucosal lining is lacking and will not easily be achieved in a cartilage tube. When tracheal homografts are used, a prompt avascular necrosis with graft expulsion will occur. No vascular pedicle can reasonably be obtained to provide revascularization of such a graft by direct microvascular suture.

More recently, autogenous materials such as free revascularized bowel segments[8] and esophageal interposition[9] have been tried to repair tracheal segments.

These techniques show an inherent absence of structural support, but their well-vascularized mucosal layer is responsible for the observation that the anastomosis healed fully without granulation tissue formation. The preformed tracheal tubes on the vascularized fascia display a fully revascularized circumferential mucosal layer (Fig 5B). Of interest is the observation that the longitudinally applied cartilage strips are capable of preserving 79% of the reconstructed lumen after a follow-up period of 4 weeks. After 2 months 86.6% of the tracheal lumen area is preserved, in contrast with only 10.7% lumen preservation in the control group. Autogenous cartilage applied longitudinally seems effective in supporting a circumferential tube when placed between the 2 layers of the fascial flap.

Fibroconnective tissue holds the cartilage strips in place even after a short period of 4 weeks. When perichondrium is included, production of new cartilage cells via appositional growth is ensured. Cartilage bridges filling the space between 2 adjacent cartilage strips are formed through the same mechanism of appositional growth.

The place in which most of the tracheal lumen is lost after removal of the silicone tube is the "membranous" region, where the fascia enters and leaves the tube.

Cartilage autografts are preferable to restore external support. They do not bear the risks of extrusion, as do alloplastic implants. Preserved cartilage allografts have generally been disappointing, as gradual, progressive cell death and finally absorption occur.[10]

Unlike bone, autogenous cartilage grafts are indifferent to functional stress for survival and they retain long-term form and bulk if an adequate vascular pocket is provided. They have not only demonstrated long-term success, but have been found to grow in size.[10-13]

CONCLUSION

Autogenous cartilage grafts applied in a vascular bed are effective in supporting a reconstructed airway wall, as evidenced by the 90% circular lumen preservation of longitudinal cartilage strips after 2 months.

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[‡] In some studies, mild nasopharyngeal irritation has been reported in up to 24% of patients treated with beclomethasone dipropionate aqueous spray. Transient nasal burning and stinging were reported in approximately 45% of patients treated with flunisolide spray.

[§] Nasalide is a registered trademark of Syntex Laboratories, Inc.; Beconase is a registered trademark of Allen & Hanburys.

Reference: 1. Bronsky EA, Tarpay M, Tinkelman DA, Bush JK. A comparison of two dosing regimens of beclomethasone dipropionate aqueous nasal spray and flunisolide nasal spray in the treatment of acute seasonal rhinitis. *Immunol Allergy Pract.* 1987;9(5):165/11-170/16.

Please see next page for brief summaries of full Prescribing Information.

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INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients being treated with VANCENASE AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use VANCENASE AQ Nasal Spray at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of VANCENASE AQ Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions carefully.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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For Nasal Inhalation Only

BRIEF SUMMARY

(For full Prescribing Information see package insert)

INDICATIONS AND USAGE VANCENASE POCKETHALER Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

VANCENASE POCKETHALER Nasal Inhaler is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies in seasonal and perennial rhinitis have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, VANCENASE treatment should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. VANCENASE treatment should not be used in the presence of untreated, localized infection involving the nasal mucosa.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE POCKETHALER Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients, previously treated for prolonged periods with systemic corticosteroids, are transferred to VANCENASE POCKETHALER Nasal Inhaler. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE POCKETHALER Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE POCKETHALER Nasal Inhaler may suppress HPA function.

VANCENASE treatment should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE POCKETHALER Nasal Inhaler to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE Nasal Inhaler should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of the VANCENASE product into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE treatment over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrus cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrus cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE POCKETHALER Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and in long-term open studies in patients treated with VANCENASE Nasal Inhaler are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children.

Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. (See **PRECAUTIONS**.)

Transient episodes of epistaxis or bloody discharge from the nose have been reported in 2 per 100 patients.

Ulceration of the nasal mucosa has been reported rarely.

Extremely rare instances of nasal septum perforation have been reported following the intranasal application of aerosolized corticosteroids. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm have been reported following the oral and intranasal inhalation of beclomethasone.

Increased intraocular pressure has been reported rarely. (See **PRECAUTIONS**.)

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome could occur.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of VANCENASE POCKETHALER Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate; therefore acute overdosage is unlikely.

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AIRWAY PROTECTION DURING BREATH-HOLDING

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Little is known about laryngeal function during breath-holding. The completeness of laryngeal closure during breath-holding is clinically relevant during the supraglottic swallow. To investigate this phenomenon, vocal cord position was studied prospectively in 10 adults during breath-holding using nasolaryngoscopy with video recording. The position of the vocal cords was not consistent during breath-holding. Some subjects closed the glottis, while others had variable amounts of glottic opening. Straining and vocalizing at the onset of breath-holding produced both glottic and supraglottic closure, increasing the number of levels of laryngeal closure during breath-holding. Nasolaryngoscopy can be used clinically to document the airway protection, the effects of various protective maneuvers, and any resulting aspiration during breath-holding and during the supraglottic swallow.

KEY WORDS — apnea, breath-holding, laryngeal closure, nasolaryngoscopy, supraglottic swallow.

INTRODUCTION

Laryngeal closure is a critical mechanism affording airway protection during swallowing. Radiographic studies have suggested that it involves the sequential approximation of the true vocal cords and false vocal cords and apposition of the arytenoids and the epiglottis.[1-5] True vocal cord closure has been shown to be one of the earliest-occurring components of the swallow synergy.[6]

Normally, laryngeal closure, and hence airway protection, only occurs during the pharyngeal phase of deglutition. Some patients aspirate before the pharyngeal phase of deglutition because of either uncontrolled spillage from the oral cavity or a delayed pharyngeal phase.[7] The supraglottic swallow may help these patients by producing airway protection before the pharyngeal phase of deglutition.[7] The technique involves holding the breath prior to deglutition, and then coughing at the completion of the swallow. The purpose of holding the breath is to actively produce laryngeal closure in an effort to reduce aspiration. Nevertheless, it has never been proven that vocal cord adduction is consistently achieved when individuals are instructed to hold their breath. In fact, Martin et al[8] recently reported that the degree of laryngeal valving associated with breath-holding varied across subjects. The valving function of the true vocal cords during breath-holding is likely to be even more important after supraglottic laryngectomy when the epiglottis, aryepiglottic folds, and false cords are resected. In order to further investigate this phenomenon, the present study examined the presence and extent of laryngeal closure associated with breath-holding by means of video nasolaryngoscopy.

A second question concerns whether laryngeal valving associated with breath-holding can be enhanced by the simultaneous use of maneuvers that promote vocal cord adduction. For example, a number of "bearing down" exercises have been employed in the treatment of hypofunctional voice disorders in attempts to increase vocal cord adduction.[9,10] These techniques also may enhance laryngeal closure during breath-holding. In order to address this issue, the present study examined whether laryngeal closure during breath-holding is increased when maneuvers that promote vocal cord closure are simultaneously employed.

METHOD

Ten healthy volunteers, 7 men and 3 women, served as subjects. They ranged in age from 21 to 34 years, with a mean age of 27 years. All subjects were recruited from the Department of Otolaryngology, Mount Sinai Hospital, Toronto, and all gave their informed consent to participate in the study.

Video Nasolaryngoscopy. With the subject seated, topical anesthesia (5% cocaine) was applied to the nasal cavity through which the laryngoscope was to be passed. Care was taken to avoid anesthetizing the pharynx. Approximately 5 minutes later, a Pentax nasolaryngoscope was passed transnasally and advanced such that its head was positioned at the level of the epiglottis. This permitted viewing of the true

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Winner of the Inaugural Glaxo Award for the best poster at the 46th Annual Meeting of the Canadian Society of Otolaryngology–Head and Neck Surgery, Quebec City, Canada, June 10, 1992.

and false vocal cords, corniculate and cuneiform cartilages, aryepiglottic folds, and epiglottis. Laryngoscopic images were recorded at 30 frames per second with a Sony Betamax video recorder and displayed on a Sony Trinitron monitor. A xenon light source was required to provide adequate illumination.

Experimental Protocol. Prior to introduction of the nasolaryngoscope, the subject was trained on 3 experimental tasks that were subsequently performed with the laryngoscope in place.

1. The first experimental task involved relaxed breath-holding only. The subject was instructed as follows, "Hold your breath for 5 seconds, and indicate when you begin and end breath-holding by raising your hand."

2. The second task, straining, involved simultaneous breath-holding and "bearing down," which the subject achieved by pulling up on the underside of the chair. The corresponding instruction to the subject was, "Grasp the underside of your chair with both hands and pull up effortfully as you begin holding your breath."

3. The third task involved breath-holding and effortful vocalization. The subject was instructed to "exhale a little and then produce an effortful 'ah' as you begin breath-holding."

Each subject initially performed 3 breath-holding trials, after which 2 trials of both of the combined breath-holding–maneuver tasks were performed in random order.

Data Analysis. The videotaped laryngoscopic images were analyzed by 4 otolaryngologists who were naive to the purpose of the study and blinded to the order of the experimental tasks. The position of the true vocal cords and false cords and amount of aryepiglottic fold–epiglottis contact were each graded separately for each breath-hold. That is, the true or false vocal cords were graded as open (grade 1), partially closed (2), completely closed (3), or not visualized (4). For aryepiglottic fold–epiglottis contact, grade 1 indicated no movement of the cuneiform and corniculate cartilages, grade 2 was an anterior tilt of the cuneiform and corniculate cartilages, and grade 3 was complete approximation of the aryepiglottic folds against the epiglottis. Each breath-hold was replayed until the otolaryngologist was satisfied with his rating. In cases in which closure at one level obscured closure below, the otolaryngologist was asked to estimate the function of the lower level.

Ratings of laryngeal closure obtained from the 4 judges were submitted to statistical analyses using the matched-pair Wilcoxon test, with $p < .05$.

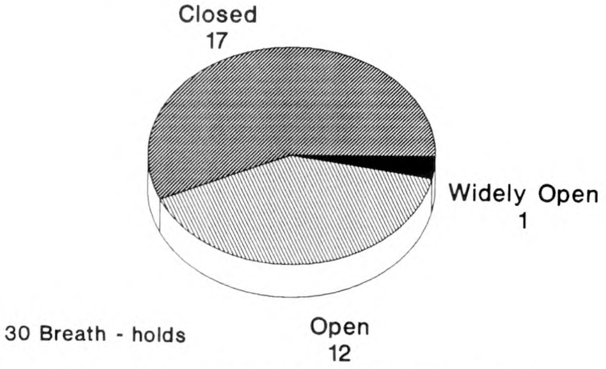

Fig 1. Glottic patency during relaxed breath-holding.

RESULTS

Overall, interjudge agreement on ratings of laryngeal closure was 80%. Interjudge agreement for ratings of true cord closure, false cord closure, and aryepiglottic fold–epiglottis contact were 91%, 69%, and 80%, respectively.

Complete vocal cord closure occurred in 17 of 30 (57%) of the breath-holds (Fig 1), and only 3 of the 10 patients had true cord closure on all 3 breath-holds. In 2 of 30 (7%) of the breath-holds there was true cord and false cord closure, providing 2 layers of defense. In 1 of 30 (3%) cases there was true cord, false cord, and aryepiglottic closure, providing 3-layered defense.

Using the straining and the vocalization maneuvers resulted in true vocal cord closure in every instance (100% of breath-holds). True vocal cord closure was significantly greater during the maneuvers than during breath-holding alone (matched-pair Wilcoxon test, $p < .05$). Furthermore, the maneuvers recruited false cord and aryepiglottic fold closure, increasing the number of levels of laryngeal closure during the breath-hold (Fig 2). The numbers of levels of closure associated with both 1) vocalization and 2) straining were significantly greater than that associated with breath-holding alone (matched-pair Wilcoxon test, $p < .05$). The vocalization maneuver provided the most reliable method of maximizing laryngeal closure, although the difference between the numbers of levels of closure during straining and vocalization maneuvers did not reach statistical significance.

DISCUSSION

Although laryngeal functions have been studied extensively during phonation and respiration, little is known about laryngeal physiology during breath-holding. Laryngeal valving during phonation and respiration occurs at a single level: the true vocal cords. Valving during normal swallowing occurs at 4

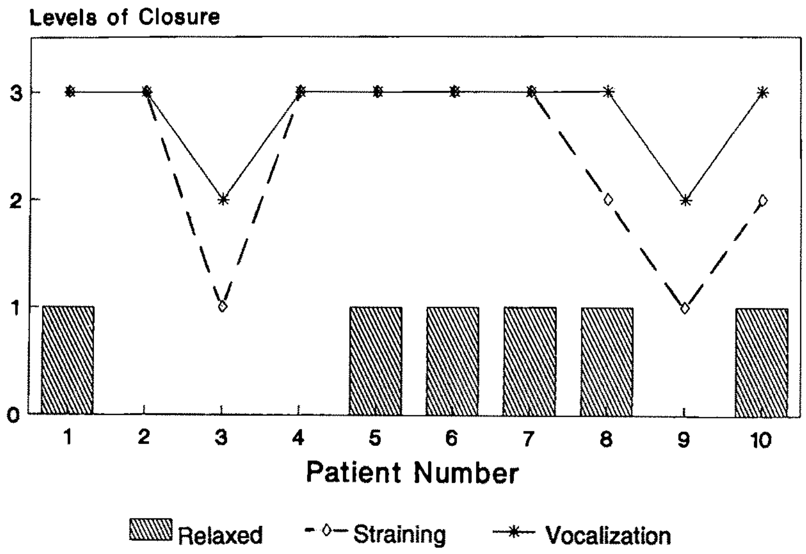

Fig 2. Number of levels of laryngeal closure with breath-holding and maneuvers (average values).

levels: true vocal cord, false cord, and aryepiglottic fold closure are augmented by epiglottic retroversion.[1-5]

This study evaluated the valving mechanism that occurs during normal breath-holding. Augmentation of the laryngeal valving mechanism during breath-holding may improve function during the supraglottic swallow. This maneuver involves breath-holding before deglutition, and coughing after the swallow.[7] It is based on the assumption that laryngeal closure, with prevention of aspiration, occurs during breath-holding.

Laryngeal valving during breath-holding in normal subjects is frequently incomplete. In this study, glottic closure (single-level protection) occurred in all 3 breath-holds in only 3 subjects. In all 10 subjects the completeness of airway closure was improved by using either a vocalization or a straining maneuver. These maneuvers ensured glottic closure in every case (100%). Furthermore, they provided closure at other levels — the false cords and the aryepiglottic folds — to augment true cord closure.

Although three-layered closure was frequently achieved by using the breath-holding maneuvers, epiglottic downfolding, the fourth level of laryngeal valving that occurs during the pharyngeal phase of deglutition, could not be produced in any case despite intense supraglottic contraction. This is in agreement with the supposition that epiglottic retroversion occurs secondary to swallow-related laryngeal elevation and bolus delivery.[11,12]

The study relied on subjective ratings for very complex and rapid events. Judges reported difficulty in endoscopic assessment of a level that was obscured by a closed level above. Closure of the lower levels occurring prior to closure of the upper levels permitted assessment of multiple levels on slow-motion evaluation. The judges assumed that closure of the false cords was associated with closure of the true cords, as the true cords are highly innervated for adduction. The grading of complete closure remained subjective and was not validated by objective leakage testing.

The nasolaryngoscope is a useful means to illustrate the extent of laryngeal closure, which varied in each subject and frequently varied between swallows. The extent of this variability in normal subjects suggests that video nasolaryngoscopy may serve as a useful means of biofeedback in patients with disordered function. After the data collection was completed, all the subjects were intrigued by seeing the result of different maneuvers on their laryngeal function.

The high variability of laryngeal valving during breath-holding in normal subjects suggests that video nasolaryngoscopy should be undertaken in all patients who are taught the supraglottic swallow. Laryngeal function during breath-holding in the abnormal larynx is unknown. Video nasolaryngoscopy would permit classification of the extent of laryngeal valving, visual feedback, and assessment of the best maneuver to improve the strength and reliability of valving.

CONCLUSIONS

1. There are 3 potential layers of airway defense during breath-holding: the true vocal cords, the false vocal cords, and aryepiglottic fold–epiglottis closure.

2. Many subjects do not close the glottis during breath-holding.

3. Vocalization or straining maneuvers strengthen

laryngeal closure during breath-holding at all 3 levels.

4. Laryngeal closure maneuvers should be employed when teaching the supraglottic swallow.

5. The pattern of laryngeal closure can be assessed by nasolaryngoscopy.

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TWENTY-NINTH POSTGRADUATE COURSE IN EAR SURGERY

The 29th Postgraduate Course in Ear Surgery will be held April 10-15, 1994, in Nijmegen, the Netherlands. For more information, contact Prof dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax 80-540251.

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FOURTH RESEARCH WORKSHOP ON THE BIOLOGY, PREVENTION, AND TREATMENT OF HEAD AND NECK CANCER

The Fourth Research Workshop on the Biology, Prevention, and Treatment of Head and Neck Cancer, sponsored by the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons, will be held in Arlington, Virginia, on September 8-11, 1994. For further information, contact We Plan Meetings, Inc, Ruth C. Enquist, President, 1503 15th St NE, Rochester, MN 55906; telephone (507) 285-1523; fax (507) 281-8328.

Ann Otol Rhinol Laryngol 102:1993

LATE WAVES IN THE RESPONSE RECORDED FROM THE INTRACRANIAL PORTION OF THE AUDITORY NERVE IN HUMANS

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We showed in previous studies that the click-evoked responses from the exposed eighth nerve in some patients contain quasiperiodic components that appear in the interval between 4 and 16 milliseconds after the click stimulus, and that the phase of these oscillatory components reverses when the click polarity is reversed. When the responses to clicks of opposite polarity are subtracted from each other, these late waves appear as a prolonged quasiperiodic oscillation with a frequency around 700 Hz. These late components appear more frequently in patients with high-frequency hearing losses than in patients with normal hearing. We have attributed these components to prolonged and in-phase oscillations of a large portion of the basilar membrane, possibly caused by the generation of standing waves on the basilar membrane. The results of the present study show that these oscillations correspond closely in both frequency and phase to the late oscillations that are seen in the cross-correlograms of the responses from the exposed eighth nerve to pseudorandom noise. The finding that similar quasiperiodic components can be retrieved from the responses from the exposed eighth nerve to both transient and continuous sounds is taken as an indication that the neural activity that these components represent reflects some general property of the cochlear frequency analyzer. We also found that the speech discrimination is not noticeably different in patients with such waves compared with what it is in patients with similar hearing loss who do not have such waves. This is taken as an indication that spectral analysis in the cochlea is less important in speech discrimination than previously assumed. The importance of timing of auditory nerve activity for speech perception is indicated by the finding that surgical trauma of the intracranial portion of the auditory nerve that only causes a moderate degree of deterioration of the pure tone threshold reduces speech discrimination scores to zero.

KEY WORDS — auditory nerve, cochlear mechanics, evoked potentials, intraoperative recordings.

INTRODUCTION

We previously showed that in some individuals there are stimulus-evoked components that occur in the compound action potentials (CAP) recorded from the exposed eighth nerve to click sounds that have a much longer latency than that of the initial 2 negative peaks.[1,2] These late components in the CAP consist of quasiperiodic waves that have a duration as long as 16 milliseconds and that occur after a click stimulus. These oscillations occur more frequently in patients with high-frequency hearing losses, but they are occasionally seen in patients with normal hearing.[1,2] In patients with high-frequency hearing loss a broad, negative peak is often seen in the response to click sounds at latencies of about 8 milliseconds.[2,3] This peak dominates the response at lower stimulus intensities, and in patients who have late oscillations in their CAP these oscillations are seen superimposed on this slow component.[2]

The phase of these late components reverses precisely when the polarity of the click stimulation is reversed, and when the responses to clicks of opposite polarity are subtracted the initial two negative peaks cancel out more or less completely, leaving these late components a nearly sinusoidal waveform. Because of the relatively large amplitudes of these vibrations it was assumed that they were the result of in-phase vibration of a large section of the basilar membrane.[2]

In other studies we found that the cross-correlograms of the responses recorded from the exposed eighth nerve using pseudorandom noise had reproducible components at delays as long as 15 milliseconds in some patients.[4] These results were interpreted as showing that there is neural activity in the auditory nerve that is phase-locked to the waveform of a continuous sound at delays as long as 15 milliseconds.

We have also presented evidence that both the late waves in the response to click sounds and the oscillatory components in the cross-correlograms of the response to pseudorandom noise represent propagated neural activity in the auditory nerve, because they appear later in time when the recording electrode is moved from a distal to a more proximal location on the intracranial portion of the eighth nerve.[1,4]

In the present study we compared results obtained in response to click sounds to results obtained in response to continuous pseudorandom noise in patients who had late components in their CAP recorded from the eighth nerve, and we present a hypothesis for the generation of these waves. We also compare the speech discrimination of patients who have such waves with that of patients who have a

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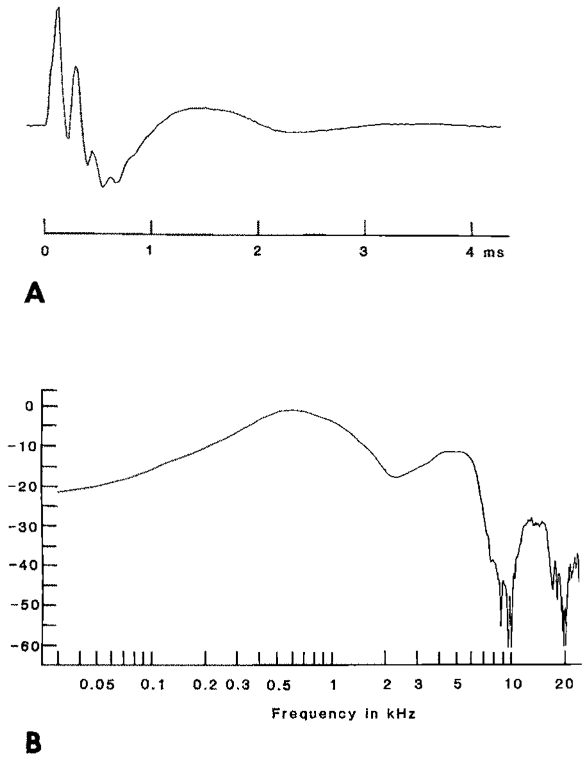

Fig 1. A) Waveform of acoustic click as recorded at entrance of ear canal of human subject using 1/4-in Bruel & Kjaer condenser microphone. B) Spectrum of click sound measured in way similar to that done in A.

similar hearing loss but no such waves.

METHODS

The results reported in this paper were obtained from recordings made from the exposed eighth nerve in patients who were undergoing microvascular decompression (MVD) of lower cranial nerves (nerves V, VII, VIII, and IX) for treatment of trigeminal neuralgia (TN), hemifacial spasm (HFS), disabling positional vertigo (DPV), tinnitus, or glossopharyngeal neuralgia (GPN). We studied the results of 35 patients from whom recordings were made using both click stimuli and pseudorandom noise under identical recording conditions. The results regarding the responses to pseudorandom noise of some of these patients were reported in an earlier paper,[4] and the responses to click sounds from some of the patients were reported by Møller and Jho.[1,2] The recording technique was previously described in detail,[1,4-6] and so only the highlights of this recording technique will be presented here.

In brief, a monopolar electrode was placed on the exposed intracranial portion of the eighth nerve while click sounds or continuous pseudorandom noise were presented to the ear through miniature stereo earphones. The reference electrode was placed on the opposite earlobe or the shoulder, and the potentials were amplified and filtered with electronic filters with cutoffs at 3 or 10 Hz (high pass) and 3 kHz (low pass). The filters had slopes of 6 dB per octave and 24 dB per octave, respectively.

We determined the root mean square (RMS) value of the difference between the response to clicks of opposite polarity in the latency interval 4 to 10.24 milliseconds. The difference was digitally high-pass-filtered with a zero-phase filter. The RMS value of the sum of the responses to clicks of opposite polarity was determined in the interval 0 to 10.24 milliseconds after presentation of the click stimuli.

Click sounds were generated by applying 100-microsecond rectangular waves to the earphones. The sound level measured at the entrance of the ear canal in a subject with normal hearing was 105 dB peak equivalent sound pressure level (Pe SPL) using a 1/4-in condenser microphone (Bruel & Kjaer type 4135) and a measuring amplifier (Bruel & Kjaer type 2601). The sensation level of the clicks presented at a rate of 20 pulses per second was 66.0 dB (±1.9 dB in 4 subjects). The waveform of the acoustic click measured with the 1/4-in condenser microphone at the entrance to the ear canal shows a brief impulse with very little ringing (Fig 1A). The spectrum of the click sound (Fig 1B) is flat (±8 dB) from 100 Hz to 7 kHz. (The dip at 10 kHz is a result of the spectrum of the rectangular electrical impulse used to drive the earphone, the duration of which is 100 microseconds.) The pseudorandom noise was based on ternary m-sequences (with 19,682 steps) that were digitally low-pass-filtered (at an equivalent cutoff frequency of 2.5 kHz), truncated to 2,048 data points, and converted to an analog signal by an LSI 11/73 microprocessor with a 12-bit digital-to-analog converter with a sampling interval of 80 microseconds. The analog signal was low-pass-filtered (at a cutoff frequency of 3,400 Hz).[6] The intensity of the noise was measured in a 2-cm^3 coupler with the same 1/4-in condenser microphone noted above, and the value is given in decibels sound pressure level. Although there were few anomalies in the pseudorandom noise used in these studies, we wanted to ensure that the different components that appear in these correlograms did not result from such anomalies. We therefore obtained responses to two different noise sequences in these studies.

The responses to noise were filtered and amplified in the same way as the responses to clicks, and they were averaged (with the same LSI 11/73 microprocessor) with the averager locked to the periodicity of the noise. For the purpose of comparing the responses to pseudorandom noise with the responses to clicks, circular cross-correlations of the recorded potentials

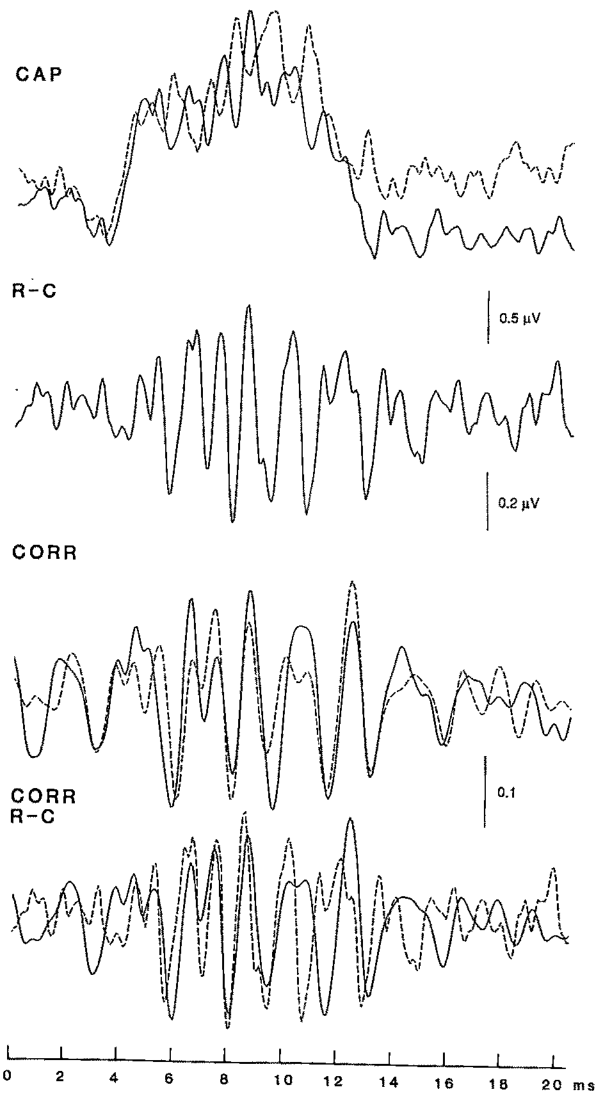

Fig 2. Typical responses obtained from middle portion of intracranial part of human eighth nerve to clicks, and cross-correlograms of responses to pseudorandom noise. Compound action potentials (CAP) were recorded with monopolar electrode, placed at location about halfway between porus acusticus and brain stem, in response to rarefaction clicks (solid lines) and condensation clicks (dashed lines). Stimulus intensity was 105 dB peak equivalent sound pressure level (Pe SPL). Negativity is shown as upward deflection. R-C is difference between responses to clicks of opposite polarity. Negative response to rarefaction click is shown as upward deflection. Cross-correlograms (CORR) of responses to pseudorandom noise were based on 2 different ternary sequences (solid and dashed lines). CORR R-C is correlation (solid line) compared with difference between response to condensation and rarefaction (dashed line). Noise was presented at intensity of 85 dB SPL, and recording was obtained from same location on intracranial portion of eighth nerve as CAP. Upward deflection indicates positive correlation between negative surface potential and rarefaction phase of noise. Patient was operated on to relieve trigeminal neuralgia and had high- and low-frequency hearing loss (25 dB at 250 Hz, 25 dB at 2 kHz, 30 dB at 3 and 4 kHz, 35 dB at 6 kHz, and 45 dB at 8 kHz).

and one sequence of the noise were obtained off-line (for details see Møller and Jho[4] and Møller[5,6]). The noise with which the responses were correlated was the sound measured in a 2-cm^3 cavity with the same $^1/_4$-in condenser microphone noted above.

Using the actual sound to determine the correlograms that were compared with the responses to click sounds provided a more accurate comparison between the time relationship of these two responses than would have been obtained if the electrical noise signal had been used as a reference.

The operative techniques for cranial nerve MVD that were used to relieve the various disorders of the patients we studied have been described previously in detail,[7-9] and therefore they will not be described here.

The procedure for this study was approved by the Institutional Review Board of the University of Pittsburgh School of Medicine, and each patient gave informed written consent to participate in this study.

RESULTS

We studied 24 patients in whom we had obtained both click- and noise-evoked auditory nerve potentials and who had late waves in either their CAP to click stimulation or in the cross-correlograms of the responses from the eighth nerve to noise stimulation. Nineteen had late components in their cross-correlograms, 15 had late waves in the CAP in response to click sounds, and 10 had late waves in both correlograms and CAP.

The frequency of these late waves measured as the inverse of the interval between two zero crossings in the same direction, around 10 milliseconds after the click stimulus, and for the correlograms, around delays of 10 milliseconds, showed mean frequencies of 759 ± 210 Hz and 853 ± 230 Hz, respectively (range, 521 to 1,316 and 408 to 1,195, respectively).

We earlier used the ratio of the RMS value of the sum and the difference between the response to clicks of opposite polarity as a measure of the relative magnitude of these late oscillations.[3] This ratio was 0.155 ± 0.076, with a range of 0.042 to 0.35 for the patients of the present study.

Figure 2 shows responses to click stimuli (CAP) and cross-correlograms (CORR) of the response to pseudorandom noise in a patient who had late waves in the CAP recorded from the exposed eighth nerve in response to click stimulation. The patient had a high- and low-frequency hearing loss. The responses to clicks of opposite polarity (CAP in Fig 2) show quasiperiodic waves of opposite phase in the interval

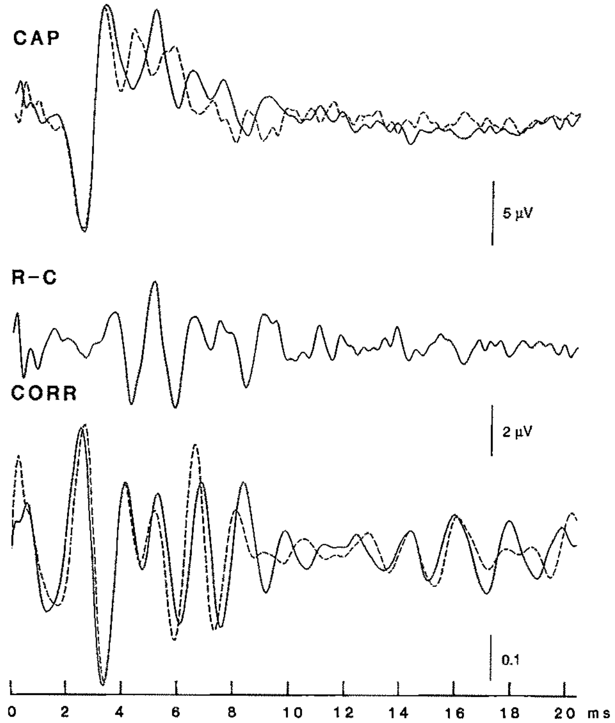

Fig 3. Recordings similar to those shown in Fig 2, but obtained in patient with late waves of shorter duration than those of patient in Fig 2. CAP are compound action potentials recorded from exposed eighth nerve. Clicks were presented at intensity of 105 dB Pe SPL. R-C is difference between responses to clicks of opposite polarity. CORR are cross-correlograms of responses to click stimulation. Noise was presented at intensity of 95 dB SPL. Patient was operated on to relieve trigeminal neuralgia and glossopharyngeal neuralgia, and he had high-frequency hearing loss beginning at 3 kHz (35 dB at 3 kHz, 30 dB at 4 kHz, 50 dB at 6 kHz, and 55 dB at 8 kHz).

between 5 and 14 milliseconds after click stimulation. When these responses to clicks of opposite polarities are subtracted, the late waves appear as quasiperiodic oscillations (R-C in Fig 2). The cross-correlograms of the responses to pseudorandom noise that were obtained at about the same time as the responses to clicks were obtained (CORR in Fig 2) contain a series of similar quasiperiodic oscillations in a range of delays between 5 and 15 milliseconds. These oscillations are well replicated in the responses (represented by solid and dashed lines in CORR in Fig 2) to two different noises (which were based on two different ternary sequences).

When the tracings of the difference between the response to click stimulation of opposite polarity (R-C in Fig 2) and the sum of the two cross-correlograms of the responses to pseudorandom noise (CORR in Fig 2) are superimposed (CORR R-C in Fig 2; dashed and solid lines, respectively), it may be seen that there is a close correspondence between the late waves in the cross-correlograms and those seen in the difference between the responses to clicks of opposite polarity.

There is also good correspondence between the late components in the cross-correlograms and the late components in the CAP in response to click stimulation in patients whose late components in the CAP are of lower amplitude and shorter duration than those shown in Fig 2. However, the correspondence in these latter cases is not as precise as that seen in the former cases, as may be noted by comparing the recordings shown in Fig 3 with each other and with the recordings in Fig 2.

In patients with normal hearing the CAP in response to clicks are dominated by the N1 peak that is preceded by a small positive deflection, but there are no late components (as illustrated in Fig 4) in their CAP, and the difference between the responses to clicks of opposite polarity consists of only an initial triphasic wave that reflects the small difference in the amplitudes and latencies of the N1 component of the CAP. The cross-correlograms of the responses to noise do not reveal any later oscillatory components, either, but there is a close correspondence between the correlograms and the difference between CAP to clicks of opposite polarity (Fig 4).

When the click stimuli are subjected to spectral filtering, the amplitude of the late waves decreases when low-frequency components of the click stimuli are attenuated by high-pass filtering, whereas these late components are nearly unchanged when high-frequency components are attenuated by low-pass filtering (Fig 5). This indicates that these late oscillations are evoked by low-frequency components of the click sounds.

In order to study whether the presence of late waves in the CAP from the intracranial portion of the eighth nerve was related to speech discrimination, we compared the speech discrimination of consecutive patients who had late waves in their CAP to click stimuli with those who had no late waves. These patients were all operated on for cranial nerve vascular compression disorders by the MVD technique (TN, HFS, DPV, and GPN). We excluded patients in whom the indication for the operation was tinnitus. Of a total of 82 patients in whom we recorded click-evoked CAP (during the period between January 1, 1990, and March 1, 1992), 35 were judged to have late waves in their CAP. The average audiograms of the patients with late waves showed a larger degree of hearing loss compared to those of patients who did not have such waves (Fig 6), and the speech discrimination scores (87.1% ± 12.7% versus 93.3% ± 6.9%) were significantly lower in those patients with waves than in those without waves ($p < .05$ Wilcoxon test);

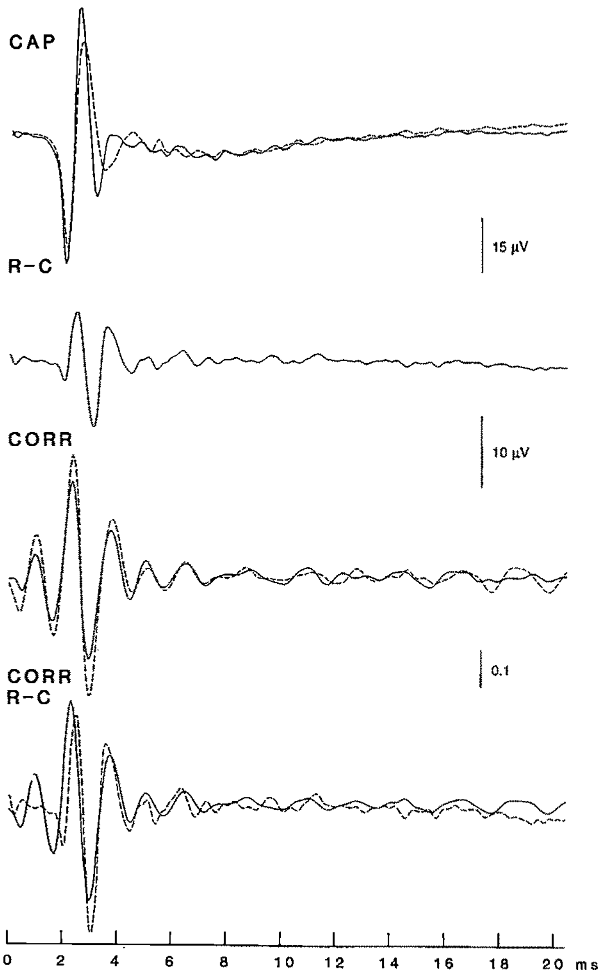

Fig 4. Typical results of recordings made from intracranial portion of eighth nerve in patients with normal hearing who did not have late components in CAP in response to click stimulation. CAP are compound action potentials recorded from exposed eighth nerve in response to clicks of opposite polarity. Stimulus intensity was 105 dB Pe SPL. R-C is difference between responses to clicks of opposite polarity. CORR are cross-correlograms of response to noise stimulation. Intensity of noise was 95 dB SPL. Patient had normal hearing and was operated on to relieve trigeminal neuralgia. CORR R-C is difference between response to clicks of opposite polarity (dashed line) and sum of correlograms shown above (solid line).

the pure tone thresholds were statistically different only for the frequencies 4,000 and 6,000 Hz ($p < .05$). When we selected patients (28) from the group without waves so that their mean audiogram matched that of the group with waves, there was no statistically significant difference ($.05 < p < .1$ Wilcoxon test) in the discrimination score (87.1% ± 12.7% versus 91.5% ± 8.0%).

These results show that the cochlear abnormalities that give rise to these waves do not impair speech discrimination significantly, which is contrary to what is the case when injuries to the eighth nerve occur (from, for instance, surgical manipulations), in which a moderate hearing loss (according to the pure tone audiogram) can result in a dramatic decrease in speech discrimination. An example of this is shown in Fig 7A, which shows the preoperative and postoperative pure tone audiograms of a patient in whom the auditory nerve was injured during an MVD operation to relieve DPV. The speech discrimination scores for this patient decreased from 96% preoperatively to 0% postoperatively. In a patient with a similar pure tone threshold (Fig 7B) the speech discrimination scores were 100% for the right ear and 92% for the left ear.

DISCUSSION

The results of the present study confirm findings of earlier studies,[1-3] that excitation of the ear with a transient sound, such as a click sound, can in some individuals result in neural activity in the auditory nerve that appears as a series of quasiperiodic waves in monopolar recordings from the exposed intracranial portion of the eighth nerve. This activity can last as long as 15 milliseconds, whereas the CAP in response to click sounds normally last only for about 3 milliseconds.

The results show that of the 19 patients with late waves in their correlograms, 10 also had waves in their click-evoked potentials, and of the 15 patients who had late waves in their CAP, 10 also had waves in their correlograms. There are several reasons why late components do not appear in both correlograms of the response to noise and the click-evoked CAP. As shown in the present paper, the late waves are mostly evoked by the low-frequency components of a sound, and the differences in the spectral content of the two sounds may be responsible for this difference.

The reason that only 10 of 24 patients showed oscillations both in the responses to clicks and in the responses to pseudorandom noise may also be related to the difference in sensitivity in detecting these oscillations in the cross-correlograms and CAP to clicks. The judgment of the presence or absence of waves was a subjective one, and when the amplitude of these waves was small, the background noise may have obscured the waves in one type of recording but not in the other. In the patients who had late waves in both click-evoked CAP and correlograms there is good agreement between the late waves seen in responses from the auditory nerve to click stimuli and the oscillations in the cross-correlograms of the responses to continuous pseudorandom noise, which indicates that these late components have the same frequency and duration.

Because the potentials that are recorded from the surface of the eighth nerve can be assumed to reflect

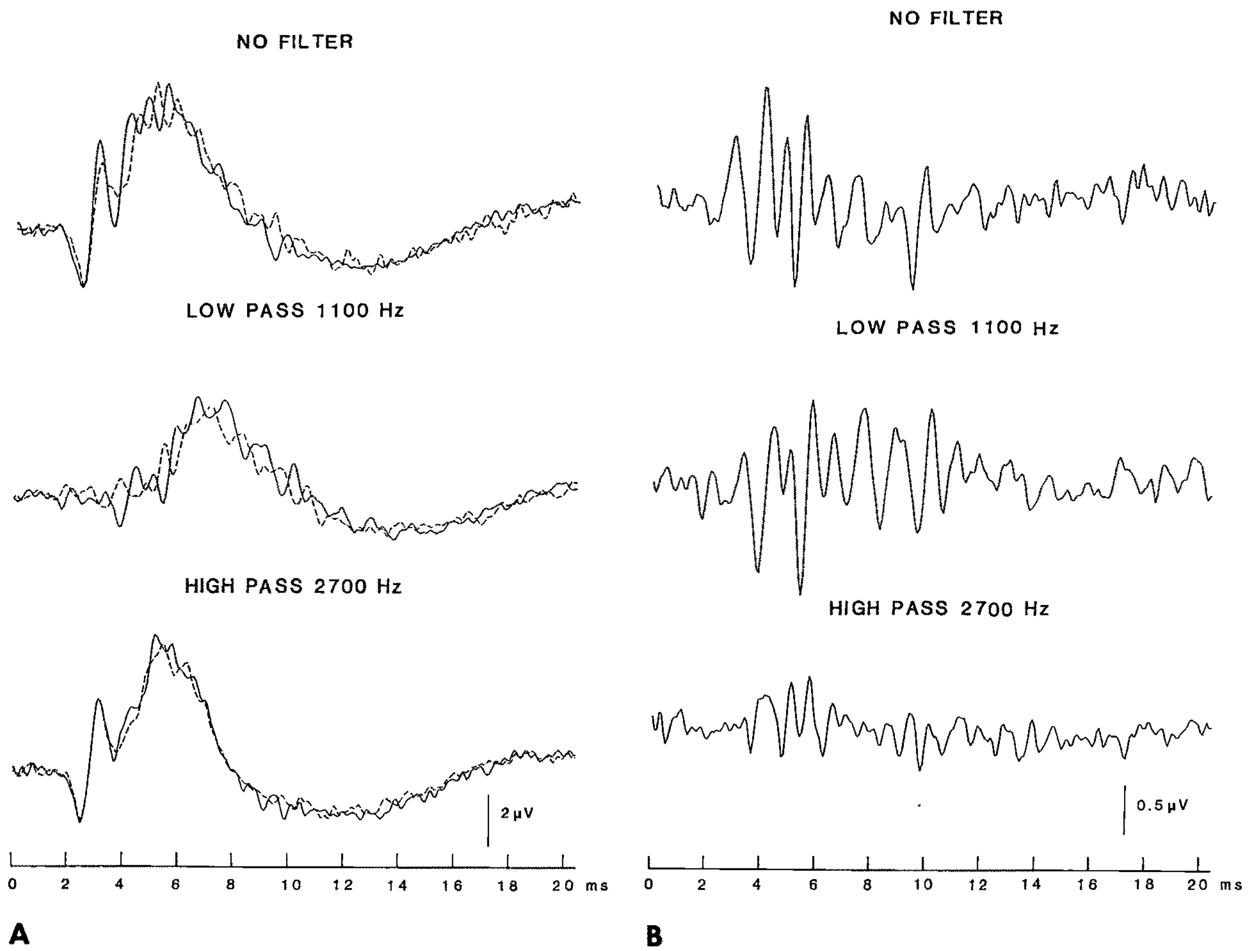

Fig 5. Effects of low-pass and high-pass filtering of click stimuli on response recorded from eighth nerve in patient who had late waves. A) CAP in response to clicks of opposite polarity. B) Difference between responses to clicks of opposite polarity. Intensity of unfiltered clicks was 105 dB Pe SPL, and slopes of filters were 18 dB per octave for low-pass filter and 36 dB per octave for high-pass filter. Patient was operated on to relieve tinnitus and had high-frequency hearing loss beginning at 4 kHz (25 dB at 4 kHz, 45 dB at 6 kHz, and 65 dB at 8 kHz).

the sum of the distributions of nerve impulses in many auditory nerve fibers,[10] the oscillatory nature of these late components in the responses to click sounds indicates that these late components represent propagated neural activity in many nerve fibers that are phase-locked to the same quasiperiodic oscillation of the basilar membrane. Thus, as has been shown earlier,[4] the oscillatory waves shift to longer delays, as do the initial components of the CAP when the recording electrode is moved from a more distal to a more proximal location on the exposed intracranial portion of the eighth nerve. It thus seems unlikely that cochlear microphonic potentials should contribute to the response, because the delay of such potentials would be the same when recorded distally or proximally along the eighth nerve. It also seems unlikely that neural activity in the cochlear nucleus would contribute to these late oscillatory potentials, because the delay of such a contribution would not change as the recording electrode was moved along the eighth nerve.

The cross-correlograms reflect the degree of resemblance between the gross potential of the auditory nerve and the waveform of the pseudorandom noise that is used as the stimulus. These two entities, the difference between the response to clicks of opposite polarity and the cross-correlograms of the response to stimulation with pseudorandom noise, thus seem to be valid measures of the phase-locking of neural activity in fibers of the auditory nerve, and the relative amplitude of these waves is a measure of the number of nerve fibers in which neural activity contributes to these waves.[10]

On the basis of comparison of the RMS value of the oscillations in the CAP to click stimuli and that of the sum of the responses to clicks of opposite polarity, we had earlier reached the conclusion that these late oscillatory components represent coherent neural activity in a large number of nerve fibers,[2] which, in turn, must mean that many hair cells are activated by the same or nearly the same frequency as these waves, thus implying that a large part of the basilar

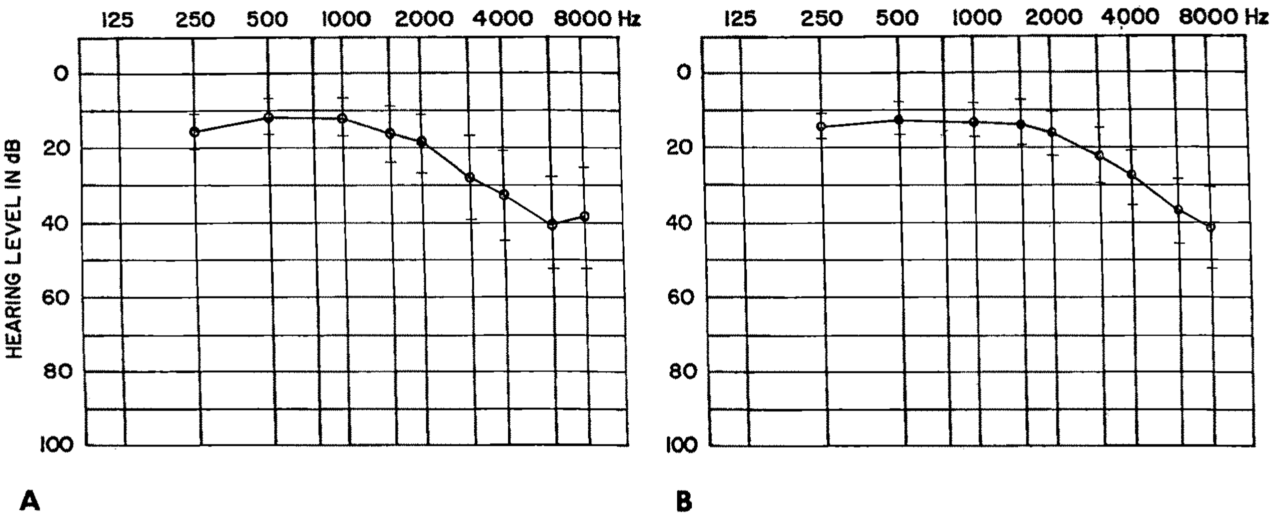

Fig 6. Averaged audiograms. A) Of 35 patients who had late waves in their CAP. B) Of 28 patients who did not have such waves. (Standard deviation is indicated by vertical bars.)

membrane oscillates with nearly the same frequency for a duration as long as 10 to 15 milliseconds. The mean value of the ratio of the RMS values of these oscillations and the sum of the CAP to clicks of opposite polarity of the patients reported on in the present study was 0.15. If we assume that a broadband click at 105 dB Pe SPL, as was used in the present study, activates all nerve fibers in the auditory nerve, then these results would mean that an average of 15% of the nerve fibers were firing synchronously to produce these oscillations. It is also obvious that the degree of this late oscillatory activation of auditory nerve fibers differs from individual to individual, because the range of this ratio was 0.04 to 0.35.

Long-lasting in-phase oscillations of the basilar membrane that could give rise to such neural excitation are not explained by contemporary models of basilar membrane mechanics, including those supporting the existence of positive feedback that may create persistent oscillations at certain locations along the basilar membrane.

The frequency of these late oscillations (around 700 Hz) could indicate that they are the result of oscillations of the portion of the basilar membrane that is tuned to frequencies around or below 1,000 Hz. This seems unlikely, however, because activation of a narrow portion of the basilar membrane would only result in activating relatively few nerve fibers. The large amplitude of these oscillations indicates that a large number of nerve fibers are activated. Also, the phase at which nerve fibers are activated by the normal traveling wave motion of the basilar membrane changes gradually along the basilar membrane, so that only relatively few nerve fibers are activated within a certain small difference in phase angle. In order to produce the large amplitude of the late oscillation in the CAP in these individuals, many nerve fibers must be activated in-phase at the same frequency. Therefore, another explanation of the generation of these waves must be sought.

If it is assumed that the outer hair cells act as a positive feedback mechanism that reduces the effect of frictional losses in the basilar membrane,[11,12] it also follows that a (small) portion of the basilar membrane can self-oscillate. This will occur if the positive feedback in a certain region of the basilar membrane becomes larger than what is needed to eliminate the effect of friction. If this happens at a certain location on the basilar membrane, then it may be that a source of vibration presented itself on its own at that location. As Zwislocki[13] has pointed out, such a localized vibration at a certain location on the basilar membrane that acts as an independent source of energy will create a wave motion on the basilar membrane that will travel in both directions from that source. The energy of the wave that travels from such a local source on the basilar membrane toward the cochlear apex will be extinguished in the same way as will a normal cochlear wave. The vibration that propagates toward the base of the cochlea, however, will be reflected when it reaches the cochlear windows because of impedance mismatch.[13] The reflected energy will create a wave that will travel toward the cochlear apex. When this wave interacts with the wave that is traveling toward the base of the cochlea, a standing wave will be created.[13]

Since such a standing wave can be expected to set large portions of the basilar membrane into vibration with the same frequency, many nerve fibers may be excited in a coherent fashion. This would explain the occurrence of late waves, such as those that we have

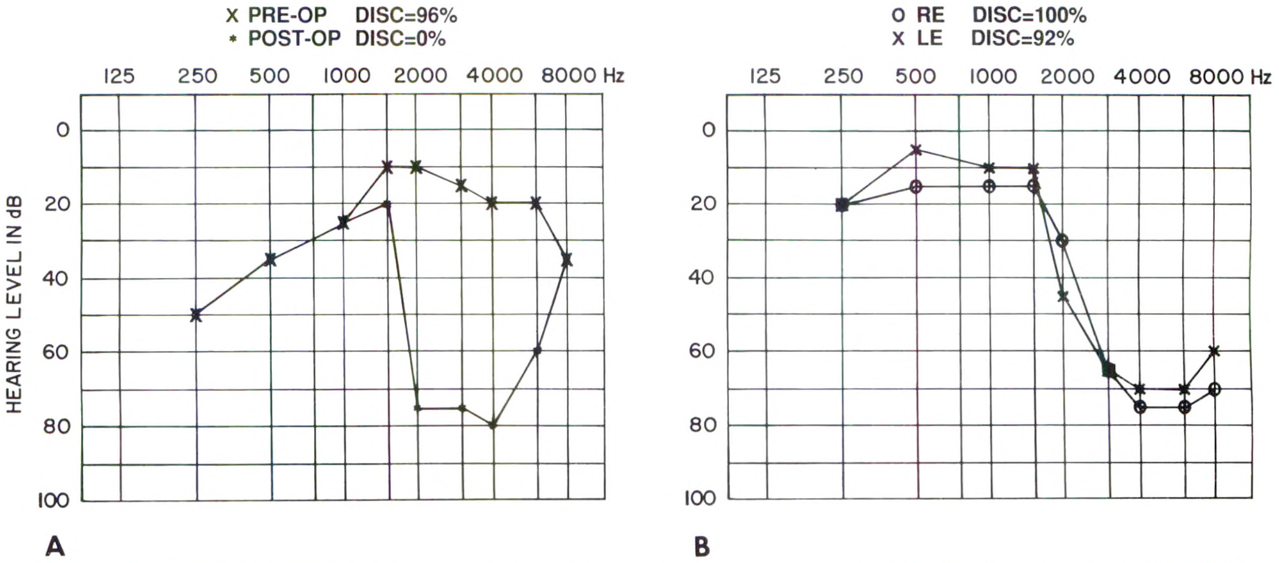

Fig 7. A) Preoperative and postoperative audiograms of patient in whom intracranial portion of auditory nerve was injured by surgical manipulation during microvascular decompression operation for disabling positional vertigo. B) Preoperative audiograms of patient with similar hearing loss of presumably cochlear origin. Patient had trigeminal neuralgia.

demonstrated in the potentials that can be recorded from the exposed intracranial position of the basilar membrane. However, Zwislocki[13] assumed that there is no reflection at the location of the energy source and therefore the duration of the standing wave would be limited. The long duration of the late oscillations in the CAP (10 to 15 milliseconds) seems to indicate that the active location on the basilar membrane may get excited again when the wave that is reflected from the cochlea windows reaches it and thus initiates a new wave.

It is not clear why these late waves occur predominantly in individuals who have a high-frequency hearing loss. Perhaps morphological changes that occur in the basilar membrane in connection with loss of hair cells in the basal portion of the cochlea may cause changes in the micromechanics of the cochlea that promote the establishment of such an independent source of energy on the basilar membrane.

To the best of the author's knowledge, similar late components have not been reported in the CAP recorded from animals exposed to noise sufficient to cause high-frequency hearing loss. This may indicate that the occurrence of these late components depends on factors other than just injury to the basal portion of the cochlea. It may be that the abnormalities that cause these late components are a result of anomalies that take a long time to develop and therefore are not present in animals that are only observed for a comparatively short time.

The existence of such late waves indicates that the traveling wave pattern on the basilar membrane is noticeably altered in individuals who have late oscillations of long duration in their CAP, and that large numbers of the fibers of the auditory nerve are not excited in accordance with a traveling wave motion on the basilar membrane, but rather as a result of a standing wave pattern that has no specific spectral analysis properties. The fact that the relative amplitude of these oscillations varies within a wide range among different individuals indicates that the standing wave motion on the basilar membrane that these oscillations are believed to reflect can have different magnitudes in different individuals. The widely varying ratio between the RMS value of these oscillations and that of the sum of the CAP to rarefaction and condensation clicks also indicates that these two types of wave motion on the basilar membrane may coexist. The relative magnitude of the standing wave may depend on the amount of the propagated energy that is reflected at a specific location along the basilar membrane. Since the traveling wave motion is assumed to be the basis of frequency spectral analysis in the cochlea, it would seem that such changes in the vibration pattern of the basilar membrane would severely disrupt the normal function of the cochlea as a spectrum analyzer. The finding of the present study, that individuals who have such waves in their auditory nerve potentials do not seem to have any noticeable deficit in perception of complex sounds as determined from their normal speech discrimination scores, may be taken to indicate that spectral analysis in the cochlea is not as important to the discrimination of complex sounds as has been previously assumed, and the results indicate that speech discrimination may rely on temporal coding to a greater extent than previously assumed. This is supported by the finding that injuries to the auditory nerve result in severe decreases in speech discrimination scores despite the impairment of pure tone thresholds of a magnitude that if caused by cochlear injuries would result in only a minimal impairment of speech discrimination. Surgically induced injury to the auditory nerve can be assumed to interfere with the timing of neural impulses in the auditory nerve because of prolongation of neural transmission that is likely to be different in different nerve fibers, whereas such trauma is not likely to interfere noticeably with the spatial distribution of neural excitation in auditory nerve fibers, thus keeping spectral representation unaltered.

Also, earlier findings in animal experiments have indicated that spectral analysis in the cochlea may be insufficient to explain the discrimination of complex sounds.[14,15] It was also found in studies of recordings of responses from single auditory nerve fibers in the rat to broadband noise that the frequency analysis in the cochlea is markedly dependent on the intensity of a sound.[5,6,16] These studies showed that not only does the frequency selectivity decrease with increased stimulus intensity, but more important, the frequency to which a certain nerve fiber is tuned is markedly dependent on the stimulus intensity.[5,6,16] That the properties of the spectral analysis of the basilar membrane change with stimulus intensity could also be inferred from the results of some of the earliest measurements of the basilar membrane motion in anesthetized animals[17] and in more recent studies in which the vibration amplitude of the basilar membrane was measured over a large range of stimulus intensities,[18] as well as from studies on recordings from single auditory nerve fibers.[5,6,16]

That the location of the maximal deflection of the basilar membrane in response to pure tones shifts toward the base of the cochlea with increasing stimulus intensity seems to constitute an obstacle in assuming that such spectral analysis in the cochlea is the main basis for frequency discrimination in the auditory system.

The results reported here were obtained in the operating room, where acoustic and electrical interference cannot be controlled to the same extent as they can in the laboratory. In addition, the time constraints associated with making recordings during operations sometimes limit the number of data that can be gathered. However, we do not believe that these constraints have noticeably affected the results obtained and reported in this paper.

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ARACHIDONIC ACID METABOLITES IN EXPERIMENTAL OTITIS MEDIA AND EFFECTS OF ANTI-INFLAMMATORY DRUGS

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Previous studies have shown that arachidonic acid (AA) metabolites are important in the pathogenesis of otitis media with effusion. The AA metabolites in 4 different experimental models for otitis media were analyzed, and the effect of anti-inflammatory drugs was studied. Purulent otitis media was induced in rats by inoculation of *Streptococcus pneumoniae* in the tympanic bulla, serous otitis media by blocking the tympanal orifice of the eustachian tube, and mucoid otitis media by combining the two procedures. Middle ear effusion was also induced by stimulating the external auditory canal with cold air. Indomethacin and hydrocortisone were used to inhibit AA metabolism in the latter model. Lipoxygenase products dominated in the purulent and cold air otitis media models. Cyclooxygenase products dominated in the mucoid and serous models. Indomethacin inhibited accumulation of middle ear effusion in the cold air otitis media model, whereas hydrocortisone did not. Apart from AA metabolites, other mechanisms and mediators appear to be responsible for the increased vessel permeability observed in the cold air otitis media model, such as interactions between mast cells and nerves in the middle ear mucosa.

KEY WORDS — arachidonic acid metabolites, cyclooxygenase products, indomethacin, hydrocortisone, lipoxygenase products, mucoid otitis media, purulent otitis media, serous otitis media.

INTRODUCTION

Arachidonic acid (AA), released from membrane phospholipids by the action of phospholipase A_2, is converted via 2 major pathways, respectively, to 1) prostaglandins (PGs), prostacyclin, and thromboxanes (Txs) and 2) lipoxins and leukotrienes (LTs). Cyclooxygenase regulates the first pathway, whereas lipoxygenase regulates the latter.[1] Phospholipase A_2 is inhibited by corticosteroids, whereas nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin inhibit the activity of cyclooxygenase.[2]

Arachidonic acid metabolites are synthesized in virtually all tissues. The half-life of the products is short, and thus they act mainly at the sites in which they are formed.[1] The AA metabolites have a wide array of actions. In inflammation, the predominant effects of the cyclooxygenase products are vasodilatation and an enhanced vasopermeability. Lipoxygenase products have also been shown to be potent increasers of vascular permeability.[1]

Prostaglandins have been identified in middle ear effusions (MEEs) of humans, as well as of experimental animals.[3-5] Studies on human and animal middle ear mucosa have revealed the presence of cyclooxygenase.[6] Injection of AA in the middle ear cavity of an animal with serous otitis media (SOM) causes a more severe inflammatory response than does SOM alone.[7] It appears that AA and its metabolites play a part in the pathogenesis of otitis media with effusion. Based on these observations, efforts have been made to characterize the AA metabolite pattern in acute and chronic forms of otitis media. In acute otitis media in humans, LTC_4 and PGE_2 are the most prominent, whereas 6-keto $PGF_{1\alpha}$ appears to be an index of chronicity.[8] In the present study, AA metabolites in 4 different experimental models for otitis media were analyzed, and the effect of anti-inflammatory drugs that modify the AA cascade was studied. Besides animal models for SOM, mucoid otitis media (MOM), and purulent otitis media (POM), an otitis media model was included in which middle ear effusion is evoked by cold air stimulation via the external auditory canal (EAC).[9] The middle ear effusion in the latter model constitutes a true transudate and has been proven useful for studies of mechanisms regulating middle ear vessel permeability and could reflect the very early events involved in production of middle ear effusion.

MATERIAL AND METHOD

Male Sprague-Dawley rats weighing 250 to 300 g

From the Department of Infectious Diseases, University of Gothenburg, Gothenburg (Goldie), and the Department of Otorhinolaryngology–Head and Neck Surgery, University of Umeå, Umeå (Hellström), Sweden; and the Department of Otolaryngology–Head and Neck Surgery, Loma Linda University Medical School, Loma Linda, California (Jung). This study was supported by grants from the Swedish Medical Council (17X-6578), the Viola and Ture Ring Foundation for Medical Research, and the Swedish Medical Association's Research Foundations.

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were used. The animals were anesthetized with methohexital (Brietal 10 mg/mL) injected into a tail vein, followed by sodium pentobarbital (Mebumal 60 mg/mL, 0.15 mL) injected intraperitoneally.

ANIMAL MODELS

Purulent Otitis Media. In 8 rats an incision was made in the ventral portion of the neck and the left tympanic bulla was dissected free. A hole was drilled in the bulla and a solution of *Streptococcus pneumoniae,* type 6A, in a dose of 2.5×10^6 colony-forming units, was inoculated through a cannula until it filled the tympanic cavity (approximately 50 µL).[10] The animals were sacrificed painlessly 3 days later.

Serous Otitis Media. In 8 rats the ventral portion of the neck was incised, the left tympanic bulla was dissected free, and a hole was drilled in the floor of the tympanic bulla. Through this a guttapercha plug (De Tray, Switzerland) was inserted into the tympanal orifice of the eustachian tube,[11] and the animals were kept for 3 days.

Mucoid Otitis Media. To induce mucoid effusion,[12] 8 animals were infected with *S pneumoniae,* type 6A, according to the procedure described above. The acute infection was allowed to resolve, and after a total of 14 days the tympanal orifice of the eustachian tube was blocked as described above for serous otitis media. The animals were sacrificed 3 days later.

Effusion Evoked by Stimulation of External Auditory Canal. In 24 animals, a stream of 14°C ± 1°C air (airflow 2.5 L/min) was blown into the left EAC for 20 minutes.[9] The animals were sacrificed promptly at the end of the stimulation.

SAMPLING FOR ANALYSIS OF ARACHIDONIC ACID METABOLITES

The animals were sacrificed with an overdose of pentobarbital (Mebumal) and decapitated, and blood was collected from the carotid vessels. Serum was prepared by low-speed centrifugation (3,000 rpm, 5 minutes) and stored at −70°C until assayed. In the POM, SOM, and MOM groups, the tympanic bulla was opened and the MEE was aspirated with a sterile syringe. The samples were stored in plastic tubes at −70°C until assayed. In animals stimulated with a 14°C airstream in the EAC, the MEE was collected as described above. The MEE of 4 animals was pooled to constitute 1 sample. Serum was pooled in the same fashion.

ANALYSIS OF ARACHIDONIC ACID METABOLITES

Reverse-phase, high-performance liquid chromatography (HPLC) was used for quantitative analysis, and radioimmunoassay (RIA) for confirmation, of all AA metabolites quantitated. The mean concentration ±SEM for each AA metabolite was calculated. The individual analysis data between the HPLC method and the RIA method were very close. After finding that the HPLC method was reliable, we did quantitative analyses by the HPLC method, and RIAs were used as confirmatory analyses.

One hundred microliters of each sample was added to 400 µL of 100% ethanol. The sample was vortexed and then centrifuged for 15 minutes at 3,000 rpm. The supernatant was recovered and concentrated to 100 µL under nitrogen gas. The ethanolic sample was dissolved in 1.9 mL of HPLC-grade water to make 5% ethanol and then eluted through a C-18 column on the Bond Elut/Vac Elut system (Analytical International, Harbor City, Calif). The C-18 column was then washed with 5 mL of HPLC-grade water. The AA metabolites retained in the cartilage were eluted with 10 mL of methanol. The methanolic eluent was dried and reconstituted with 200 µL of 50% ethanol. The sample (50 µL) was injected into the reverse-phase HPLC system (Shimadzu LC-6A with a C-R 6A data processor and an SPD-6A UV detector). The column used was a Du Pont reverse-phase, Zorbax ODS column (4.6 mm × 25 cm) with an ODS guard column (4.6 mm × 5 cm). The eluting solvent for lipoxygenase products was 70% methanol and 30% water (containing 0.1% acetic acid and 0.1% trifluoroacetic acid). The flow rate was 1.5 mL/min. The wavelength was set at 280 nm for the first 5.5 minutes, at 235 nm from 5.5 to 14 minutes, and at 280 nm from 14 to 22 minutes. The eluting solvent for cyclooxygenase products was 35% acetonitrile, 65% water (containing 0.1% of 85% hydrogen phosphate) for 14 minutes. The flow rate was 1 mL/min for 11 minutes, and from 11 to 14 minutes the flow rate was 3 mL/min. The wavelength was set at 195 nm.

For RIA, the extraction procedures described above were used. Instead of reconstituting the dried methanolic eluent with ethanol, samples were reconstituted with 5 mL of saline 0.1% gel. The RIA was carried out by a modification of the method of Niswander and Midgley.[13] Standard PGs (Sigma Chemical Co, St Louis, Mo) in concentrations from 10 ng to 0.01 ng were used. Samples, tritiated PG (New England Nuclear, Boston Mass), and antiserum to PG (donated by Dr D. Hwang, Louisiana State University, Baton Rouge, La) were added to a mini–scintillation vial and incubated overnight at 4°C. Anti-rabbit gamma globulin was added as a second antibody and incubated for 48 hours at 4°C. The samples were centrifuged, the supernatant was discarded, and the pellet was counted in a liquid scintillation counter. Concentrations of PGs were determined from the

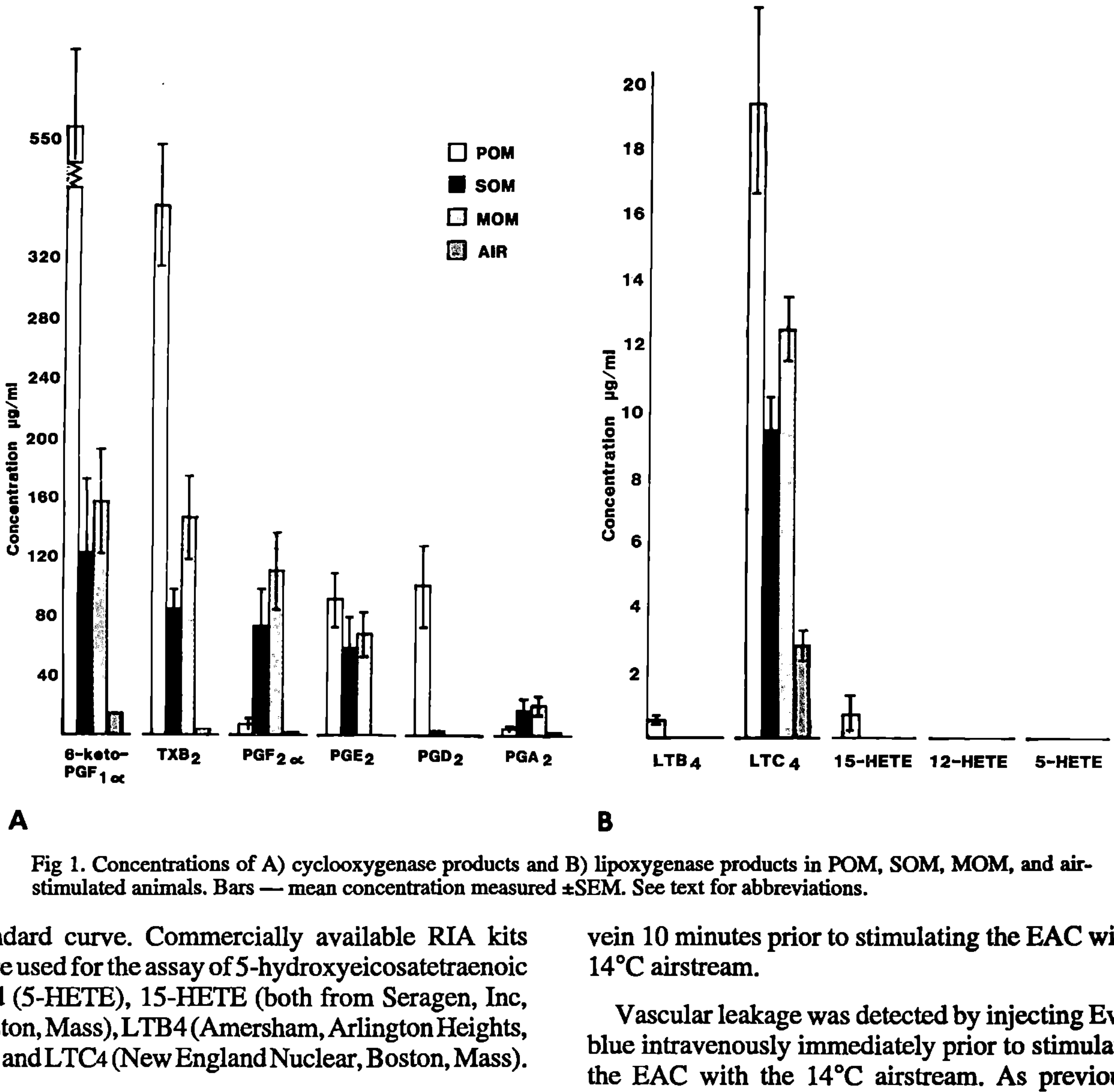

Fig 1. Concentrations of A) cyclooxygenase products and B) lipoxygenase products in POM, SOM, MOM, and air-stimulated animals. Bars — mean concentration measured ±SEM. See text for abbreviations.

standard curve. Commercially available RIA kits were used for the assay of 5-hydroxyeicosatetraenoic acid (5-HETE), 15-HETE (both from Seragen, Inc, Boston, Mass), LTB4 (Amersham, Arlington Heights, Ill), and LTC4 (New England Nuclear, Boston, Mass).

EFFECTS OF ANTI-INFLAMMATORY DRUGS

The effect of hydrocortisone and indomethacin (Sigma Chemical Co, St Louis, Mo) on the production of MEE was tested in animals stimulated with a 14°C airstream in the EAC. Hydrocortisone was dissolved in 0.9% saline to the concentrations 5, 10, 20, and 50 mg/kg body weight (bw). Hydrocortisone 5, 10, and 20 mg/kg was injected 12 and 2 hours before the start of the experiment. In addition, trials were made injecting 20 mg/kg 60 minutes before the start of the experiment, or 50 mg/kg 105 minutes before the start of the experiment.

Indomethacin was dissolved in an ethanol-phosphate buffer solution (7.5 or 15 mg/mL indomethacin dissolved in 0.5 mL ethanol and 1.5 mL 0.154 mol/L phosphate buffer, pH 7.4) to the concentrations 5, 10, and 20 mg/kg bw. Five animals were used for each concentration. Indomethacin was injected in a tail vein 10 minutes prior to stimulating the EAC with a 14°C airstream.

Vascular leakage was detected by injecting Evans blue intravenously immediately prior to stimulating the EAC with the 14°C airstream. As previously described,[9] formamide was instilled into the opened tympanic cavity at the end of the air stimulation. Three minutes later, the MEEs and formamide were collected in glass vials and stored in a refrigerator until analysis, when the samples were diluted with formamide to 1 mL. The absorbance of Evans blue was determined in a double-beam spectrophotometer (Varian DMS 100) at a wavelength of 622 nm, and the median and first and third quartiles were determined.

Statistical analysis was performed with the non-parametric Mann-Whitney test. The significance level was set at $p < .025$.

RESULTS

The samples were collected on the third day after the operations. Previous experiments have shown that this time is required for the various otitis media conditions to develop and for MEE to collect in the

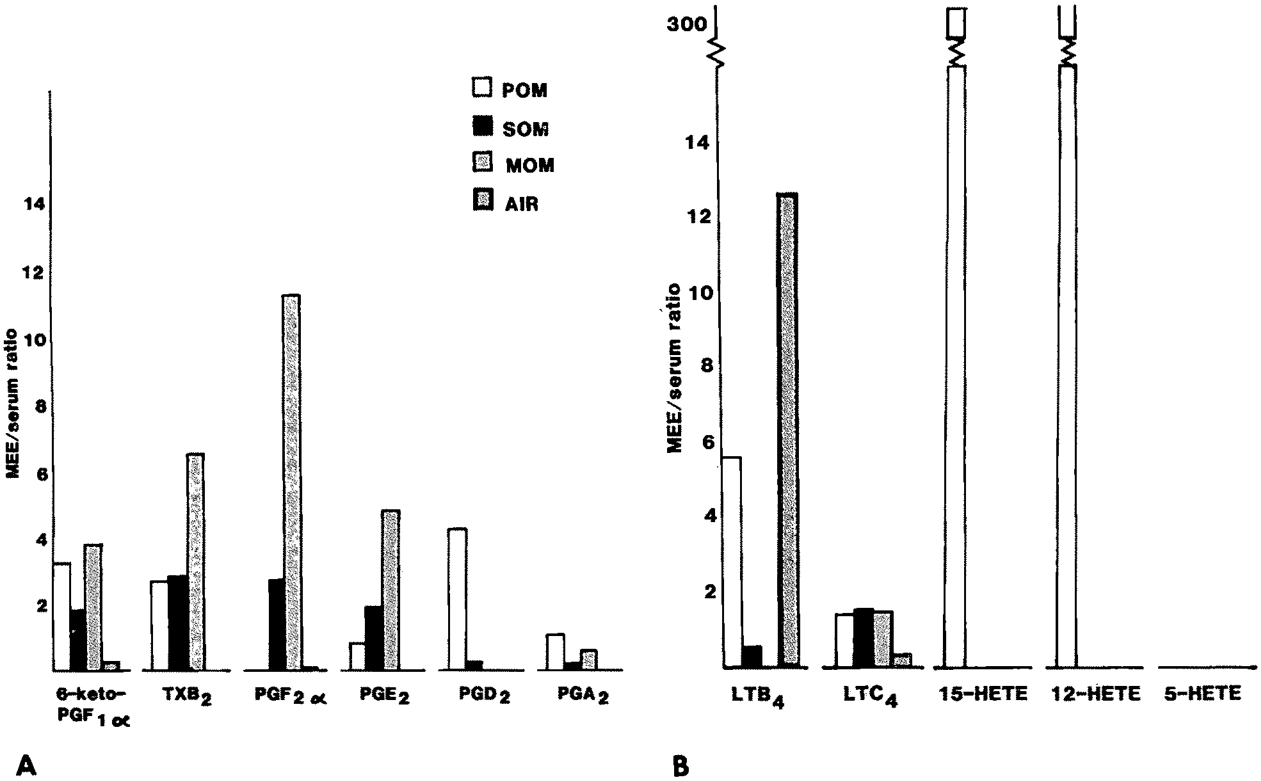

Fig 2. Middle ear effusion–serum ratio of various A) cyclooxygenase products and B) lipoxygenase products in POM, SOM, MOM, and air-stimulated animals. See text for abbreviations.

middle ear cavity. In animals stimulated with an airstream in the EAC, studies were performed directly after stimulation, since the tympanic membrane normalizes and the MEE resolves within 24 hours.[14]

OTOMICROSCOPIC APPEARANCE

Three days after inoculation of *S pneumoniae*, POM animals exhibited a retracted pars flaccida, dilated vessels, and thick, greyish effusion filling the middle ear cavity. The pars flaccida in SOM animals was retracted on day 3 and yellow, transparent fluid filled the middle ear cavity. In MOM animals, the pars flaccida was retracted on day 3 and a yellow, opaque fluid filled the middle ear cavity. The animals sacrificed 20 minutes after stimulating the EAC with a 14°C airstream displayed a slightly retracted pars flaccida and translucent fluid in the attic space.

ANALYSIS OF ARACHIDONIC ACID METABOLITES

The AA metabolites identified in MEE and serum of the various otitis media models included 6-keto PGF1α, TxB2, PGF2α, PGE2, PGD2, and PGA2 in the cyclooxygenase pathway, and LTB4, LTC4, 15-HETE, 12-HETE, and 5-HETE in the lipoxygenase pathway.

In POM animals, the metabolites present at the highest concentrations were 6-keto-PGF1α, TxB2, PGE2, and PGD2, as well as LTC4. The MEEs from SOM and MOM animals contained larger amounts of PGF2α than those from the other groups. Other prominent metabolites of the SOM and MOM groups were 6-keto-PGF1α, TxB2, PGE2, and LTC4, although concentrations were not as high as in the POM animals. The dominating metabolites of air-stimulated animals were 6-keto-PGF1α and LTC4. Overall, the concentrations were far smaller in air-stimulated MEEs than in the other groups (Fig 1).

Comparing the AA metabolites in MEE with the AA metabolites in serum demonstrated greater concentrations for most AA metabolites in MEE than in serum. The MOM animals exhibited the greatest MEE-serum ratio for TxB2, PGF2α, and PGE2. The POM animals demonstrated the greatest MEE-serum ratio for PGD2, 15-HETE, 12-HETE, and LTB4. Animals stimulated with air showed the greatest ratio for 6-keto-PGF1α, LTB4, and LTC4 (Fig 2).

EFFECTS OF ANTI-INFLAMMATORY DRUGS

There was no extravasation of Evans blue in animals treated with indomethacin 20 mg/mL bw. At the other concentrations tested, blue-stained fluid accumulated in the attic space (Fig 3A). In hydrocortisone-treated animals, an increased amount of Evans blue was found in all samples except at hydrocortisone 20 mg/kg bw administered 1 hour before stimu-

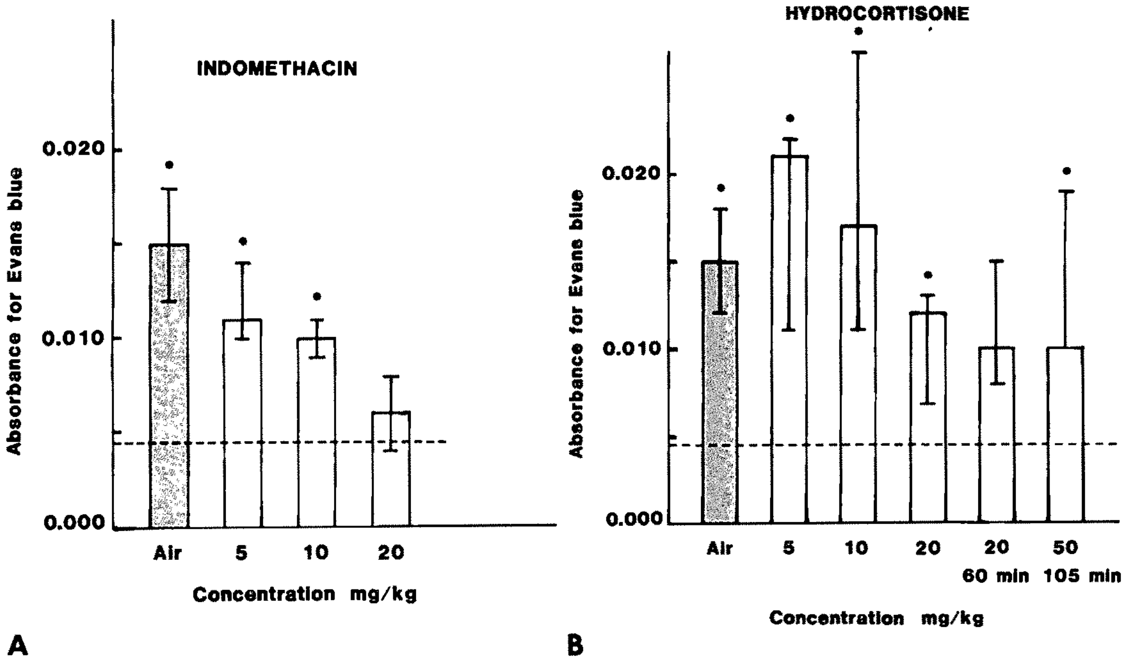

Fig 3. Vascular leakage in ears stimulated with 14°C airstream in left EAC after administration of A) indomethacin and B) hydrocortisone. Bars — median absorbance value, with first and third quartiles indicated; broken line — absorbance value for control animals; asterisk — significantly different from control animals ($p < .025$).

lation of the EAC (Fig 3B).

DISCUSSION

It is well known that AA metabolites have pronounced effects on inflammatory processes.[1,15] Studies of otitis media have revealed the presence of AA metabolites in human[3] as well as chinchilla MEEs.[4,5] In the rat otitis media models used in the present study, AA metabolites were identified in effusion material of all models. The greatest amounts of the various metabolites were found in POM animals, whereas the smallest concentrations were found in animals stimulated with cold air in the EAC. It could be assumed that AA metabolites identified in the MEEs were the result of extravasation from serum. However, the ratio between the AA metabolites in MEE and those in serum was greater than 1, indicating local production of AA metabolites in all models.

Recent findings on human MEE have demonstrated a predominance of LTC4, 15-HETE, and 12-HETE in acute forms of otitis media, whereas the MEEs from patients with MOM show great amounts of TxB2, PGE2, and PGD2 (Jung, unpublished data). In a chinchilla model for otitis media, LTC4 and PGE2 appeared to be the most sensitive indicators of acute inflammation, and 6-keto-PGF1α appeared to be an index of chronicity.[8] In regard to the MEE-serum ratio, in the rat acute otitis media model, LTB4, 15-HETE, and 12-HETE, as well as PGD2, are the most prominent AA metabolites, whereas TxB2, PGE2, and PGF2α are the dominating AA metabolites in the rat model for a long-standing inflammatory state (MOM). The present study shows that there exist interspecies variations in AA metabolism. It appears from the present and previous studies that lipoxygenase products are the major metabolites in acute forms of otitis media.[8] This corresponds to previous findings in culture-positive MEEs, in which LTB4 has been shown to be the only AA metabolite present in higher concentrations compared to culture-negative fluids.[8] Lipoxygenase products increase vascular permeability and act as neutrophil chemoattractants, which are important steps in the initial phases of the inflammatory reaction.[16] Also, lipoxygenase products have been shown to increase mucus secretion in human respiratory tissue.[17]

The present investigation, as well as previous investigations, suggests cyclooxygenase products to be the dominating metabolites in more chronic forms of otitis media.[8] Both PGE2 and PGI2 — the stable end product of which is 6-keto-PGF1α — act as vasodilators and increase vascular permeability induced by other mediators such as bradykinin.[15] Both PGE2 and PGI2 are produced by mononuclear leukocytes, and PGI2 is also synthesized by arterial endothelium. Thus, the presence of cyclooxygenase products in chronic forms of otitis media might be explained by the increased vascularity and infiltration of mononuclear leukocytes observed in the subepithelial space of chronic otitis media.[18]

The dominant metabolites in the MEE from animals stimulated with cold air in the EAC, judged from the MEE-serum ratio, were LTB4, LTC4, and 6-keto-PGF1α. The predominance of lipoxygenase products is in accordance with the idea of this model as an acute inflammatory reaction: the MEE appears within 20 minutes of stimulation and has resolved within 24 hours.[14] The high MEE-serum ratio for LTB4 in cold air-stimulated animals is notable. Although LTB4 does not possess vasodilatory activity, it contributes to bradykinin-induced plasma leakage, which is significantly increased when LTB4 is used in combination with PGE2.[19,20] It has been suggested that the vasodilation observed during an inflammatory process is caused by leukocyte accumulation and neutrophil adherence to the endothelium in response to LTB4. Vascular permeability increases as granules from neutrophils are released. This reaction is potentiated when LTB4 is released along with a potent vasodilator such as PGE2.[21]

The accumulation of MEE in the cold air otitis media model was inhibited by indomethacin, whereas hydrocortisone appeared only to have a minimal effect on middle ear fluid extravasation. Since indomethacin inhibits cyclooxygenase, it would appear that the PGs are of greater importance in fluid accumulation than lipoxygenase products. These results contradict earlier studies of the chinchilla POM model, in which the nonsteroidal anti-inflammatory drug ibuprofen seemed to stimulate middle ear fluid production, presumably through increasing the amount of lipoxygenase products.[7] In another study on antigen-induced otitis media, corticosteroids inhibited vascular leakage and leukocyte infiltration.[22] It appears that the events leading to middle ear fluid accumulation in the cold air otitis media model differ from those of other models of otitis media. Previous investigations have indicated that mast cells and their contents are important for fluid production[9,23]; cold air in the EAC releases histamine into the middle ear cavity.[24] When mast cells degranulate, prostaglandins, primarily PGD2 and PGI2, are synthesized de novo.[25] The PGI2 induces vasodilation, but is particularly potent in increasing vessel permeability induced by other mediators, such as histamine.[15] The effect of indomethacin resulting in reduction of vessel permeability in the cold air-induced otitis media model might thus be due to inhibition of PGI2 synthesis.

The very moderate effect of hydrocortisone on fluid production may be due to yet other mechanisms for increasing vessel permeability in the cold air otitis media model, such as neurogenic inflammation.[23] Peptide-containing nerves and mast cells are thought to interact, resulting in an increased flow and permeability of vessels.

This study demonstrated the AA metabolite pattern in rat models for POM, SOM, and MOM. In accordance with previous studies, lipoxygenase products appear to represent acute inflammatory reactions, whereas cyclooxygenase products seem to indicate chronicity. However, in the cold air otitis media, a model for very early inflammatory events, indomethacin inhibited middle ear fluid accumulation, whereas hydrocortisone only had minimal effects on vessel permeability. The different reaction a few minutes after onset of middle ear inflammation could be due to underlying mechanisms other than AA metabolites as mediators for increasing vessel permeability, such as mast cells and interactions with neuropeptides present in the mucosa of the middle ear cavity.

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Pamela Goldie, MD, PhD
1962-1992

The international community of otorhinolaryngologists has lost one of its brightest burgeoning stars. The foregoing article may be her last paper to be published.

The daughter of a well-known orthopedic surgeon in Stockholm, Pamela started her medical education at the University of Umeå in 1982. Being exceptionally brilliant and eager to increase her knowledge, she found that medical studies were not enough for her capacity and undertook research activities with the Ear Research Group, jointly operated by the Departments of Anatomy and Otorhinolaryngology. Her project focused on mechanisms of vascular leakage in inflammatory conditions of the ear. With Pamela's creativity, hard work, and skill she rapidly acquired the laboratory techniques and soon published her first paper on early vascular events in middle ear inflammatory conditions. She was the first to propose neurogenic inflammation as one mechanism in the production of middle ear effusion. She received an MD degree in 1987 and was awarded a PhD degree for her thesis entitled "Vascular Events in Experimental Otitis Media" in 1989. After her internship she started residency training in otorhinolaryngology at the Karolinska Hospital in 1991. Although she was ill with malignant melanoma, she continued her research interest and was investigating the complement system in otitis media induced by *Hemophilus influenzae* at the time of her death. Pamela was expected to have a splendid career in otorhinolaryngology.

Pamela was charming, warm, sensitive, and always enthusiastic. She had an enormous capacity to make friends among colleagues, national and international. Pamela will be missed dearly by many friends and colleagues, but most by her parents and sisters, with whom we share the sorrow of her early death.

Sten Hellström, MD, PhD
Timothy T. K. Jung, MD, PhD

IMAGING CASE STUDY OF THE MONTH
EXTRACRANIAL CAROTID ARTERY ANEURYSM

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The following case is presented to illustrate the importance of diagnostic imaging for complete evaluation of a nonpulsatile neck mass.

CASE REPORT

A 63-year-old man with a history of multiple medical problems related to atherosclerosis (including peripheral vascular disease of both lower extremities, coronary artery bypass grafting, and abdominal aortic aneurysm repair) presented to the emergency department with abdominal pain. Other significant history included carcinoma of the lung, non–small cell type, status post radiotherapy to the primary tumor, and an incisional hernia from previous aortic aneurysm surgery. Surgical repair of the incisional hernia was performed, with an incidental finding of adenocarcinoma in the hernial sac. The primary was not clear.

A significant physical examination finding was that of a 2- to 3-cm high cervical palpable mass in the neck. There was no pulsation, and the mass was nontender and fixed firmly. The patient stated that this had been stable in size for at least the last 3 months. It was felt that this was metastatic progression of the lung disease. However, there was clinical confusion because the lung tumor pathologic diagnosis was squamous cell carcinoma and the hernial sac pathologic diagnosis was adenocarcinoma. The patient was then seen by several oncologists, head and neck surgeons, and radiotherapists. He was advised a number of times to undergo biopsy of what was felt to be a metastatic cervical submandibular lymph node. The patient, as well as the patient's family, refused any further interventional procedure at this time.

RADIOGRAPHIC FINDINGS

Chest radiography and computed tomography (Fig 1) demonstrated a 4.0-cm spiculated mass in the

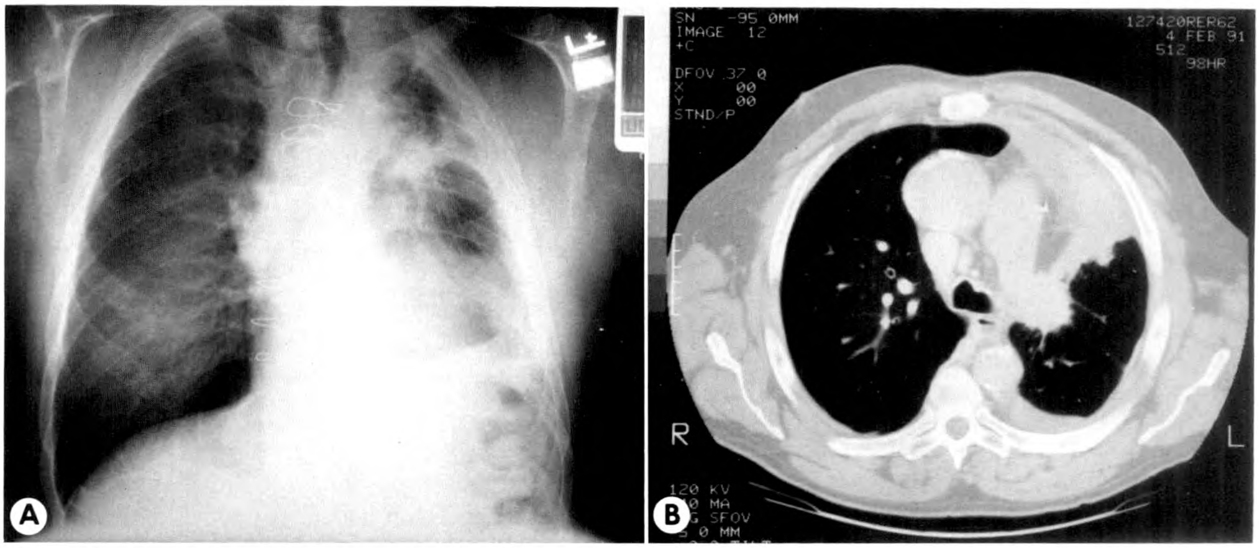

Fig 1. Images of chest. A) Posteroanterior view demonstrates spiculated mass in upper lobe of left lung with postirradiation changes. B) Computed tomogram better demonstrates known carcinomatous lesion of left lung.

From the Department of Radiology, Oakwood Hospital, Dearborn, Michigan (Beydoun, Thompson), and the Department of Radiology, Thomas-Davis Medical Center, Tucson, Arizona (Tertel).

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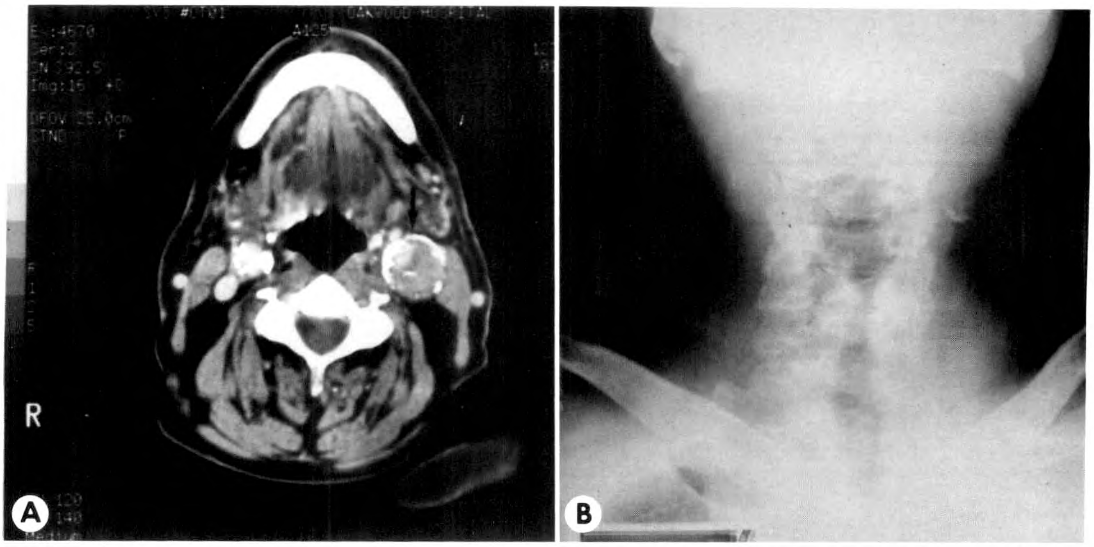

Fig 2. Images of neck. A) Computed tomogram with contrast demonstrates 3.0-cm aneurysm (arrow) of distal left common carotid artery. There is heavy calcification and intraluminal thrombus that would explain why nonpulsatile mass was palpable. B) Plain film demonstrates heavily calcified carotid aneurysm on left.

upper lobe of the left lung with peripheral pleural and parenchymal changes. These findings are compatible with the patient's history of primary lung carcinoma and postirradiation changes. After repeated patient refusal of any interventional procedure, including biopsy, a computed tomography scan of the neck was subsequently performed (Fig 2A). The significant finding was that of a 3.0-cm aneurysm of the left common carotid artery, just proximal to the bifurcation, with peripheral calcification. There was a large amount of intraluminal thrombus and a small true lumen. The right common carotid artery was also heavily calcified, with a maximal diameter of 1.5 cm just proximal to the bifurcation. No significant lymphadenopathy was identified. Subsequently, a plain radiograph of the neck in the anteroposterior projection was performed and demonstrated heavy calcification of the left common carotid aneurysm (Fig 2B).

DISCUSSION

Occlusive and ulcerative atherosclerotic lesions of the cervical carotid arteries are extremely common. Aneurysms of the extracranial carotid arteries, on the other hand, are quite uncommon, particularly in comparison with the frequency of aneurysms that occur throughout the rest of the arterial system. The common carotid artery, particularly at the bifurcation, is the most frequently reported site of aneurysm formation in the extracranial carotid system; the internal carotid is the next most common, and the external carotid is the least common location.[1] Since extracranial carotid aneurysms are rare, their true natural history is uncertain.[2] In 1926, Winslow[3] reported that the course of these lesions, when untreated, was death from rupture, thrombosis, or embolism in about 70% of cases. Further investigations have substantiated this poor prognosis.[4,5]

Several causes of extracranial carotid aneurysms have been reported. Syphilis and local infection were the most common etiologic factors 50 years ago, but are rare today.[6] Atherosclerosis is now the most frequently reported cause. The histologic features are typically atherosclerotic with disruption of the internal elastic lamina and thinning of the media. Grossly, these aneurysms tend to be fusiform rather than saccular. Most affected patients have severe arterial hypertension, and about 25% have other arterial aneurysms. Most bilateral, nontraumatic, extracranial carotid false aneurysms are atherosclerotic.[2] Trauma is another major and increasingly frequent cause of carotid aneurysms. There may be no history of trauma, nor a bruit heard, nor pulsations felt.[7] False aneurysms have been reported after carotid endarterectomy.[8] Mycotic aneurysms of the extracranial carotid arteries from adjacent peritonsillar abscess have also been reported.[3] Other documented cases of extracranial carotid aneurysms include cystic medial necrosis, Marfan's syndrome, fibromuscular dysplasia, and dissection.[2,5,9]

Clinically, a pulsatile mass is the most common presentation of an extracranial carotid aneurysm. However, if the aneurysm demonstrates heavy intimal calcification and peripheral thrombus, a firm, nonpulsatile mass will be palpated. In addition, a pulsating mass is often difficult to differentiate from the pulsations transmitted through any mass contiguous to a major vessel.[7] These aneurysms may be painful, tender, or asymptomatic. They occasionally are recognized as a pulsating tumor of the tonsillar fossa or pharynx, with little or no manifestation of their presence externally in the neck.[2]

Other clinical presentations include dysphagia, cranial nerve compression, pain, central nervous system dysfunction (cerebral ischemic episodes), and, rarely, hemorrhage.[2]

SUMMARY

Although rare, extracranial carotid aneurysms are common enough to be considered in the differential diagnosis of a mass in the neck or posterior pharynx. The unexpected finding of an aneurysm of the carotid artery during the biopsy of a mass in the neck for histologic diagnosis could be catastrophic. The case presented demonstrates the importance of diagnostic imaging of the neck prior to biopsy of a clinically presumed solid mass.

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The XXIst Congress of the International Neurootological and Equilibriometric Society will be held in Bad Kissingen, Germany, March 17-20, 1994. For further information, contact NES, Prof Dr C.-F. Claussen, Kurhausstrasse 12, D-97688 Bad Kissingen, Germany; telephone (00 49) 9 71-6 48 32; fax (00 49) 9 71-6 86 37.

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IMAGING CASE STUDY OF THE MONTH

TORTUOUS INTERNAL CAROTID ARTERY: A RARE CAUSE OF OROPHARYNGEAL BULGING DIAGNOSED BY MAGNETIC RESONANCE ANGIOGRAPHY

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INTRODUCTION

In the differential diagnosis of an oropharyngeal mass, it is crucial not to overlook an aneurysm or an aberrant great vessel. We present here a rare case of tortuous internal carotid artery (ICA) that manifested itself as a bulging of the posterior wall of the oropharynx. In this patient, who suffered from atherosclerosis, magnetic resonance angiography (MRA) allowed noninvasive visualization of the neck great vessels without the need for arterial catheterization and contrast product injection.

CASE REPORT

A 71-year-old man complained of slight throat pain and sensation of a foreign body. He was known to be suffering from atherosclerosis with ischemic heart disease and had undergone, 8 years before, a coronary angiography that had demonstrated triple-vessel disease.

The physical examination revealed a bulging of the right posterior wall of the oropharynx, behind the posterior tonsillar pillar. A closer and longer inspection clearly showed a mass, pulsating in synchrony to the pulse. An anomaly of the ICA was therefore considered.

By MRA, we visualized an abnormal course of the right ICA. On axial images (Fig 1), a great vessel was seen in the right lateral recess of the oropharynx. Processing of the images demonstrated the global projections of the vessels on axial and coronal views (Fig 2), identifying this tortuous vessel as the right ICA. The ICA usually runs straight from the carotid bulb to the base of the skull. The MRA coronal image also showed a slightly tortuous course of the left ICA, but without impingement on the pharyngeal wall.

The patient was told about the diagnosis, and no treatment was given.

DISCUSSION

Leipzig and Dohrmann[1] divided the variations in the course of the carotid artery into two categories: 1) elongation, redundancy, undulation, and an S-shape curve, which are listed under the heading of "tortuosity," and 2) a sharp bend or kink in the vessel. According to Leipzig and Dohrmann, the two main causes of these malformations are atherosclerosis and congenital deformity, and the mean age at time of diagnosis is 58.8 years.

A kink of the ICA can be associated with cerebrovascular symptoms due to alterations in cerebral blood flow. Tortuosity can cause a throbbing or occasionally painful sensation, but is usually asymptomatic and is considered a relatively benign condition.[1] However, the otolaryngologist should be aware

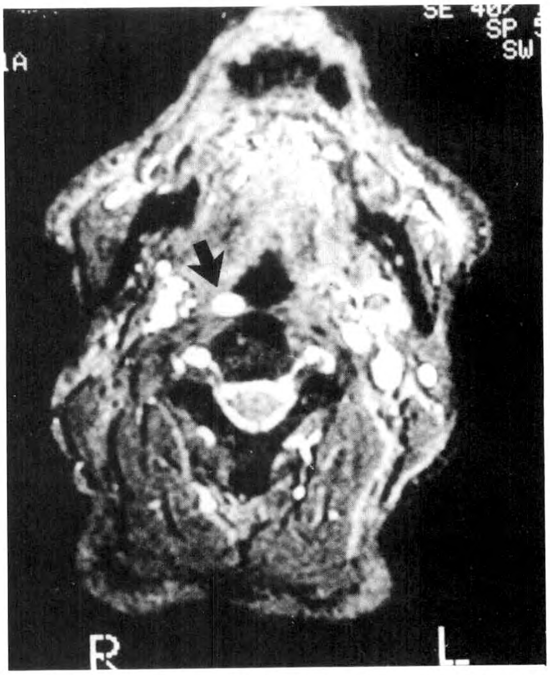

Fig 1. Axial flow-sensitive gradient-echo scan demonstrating vascular structure bulging into right retropharyngeal area (arrow).

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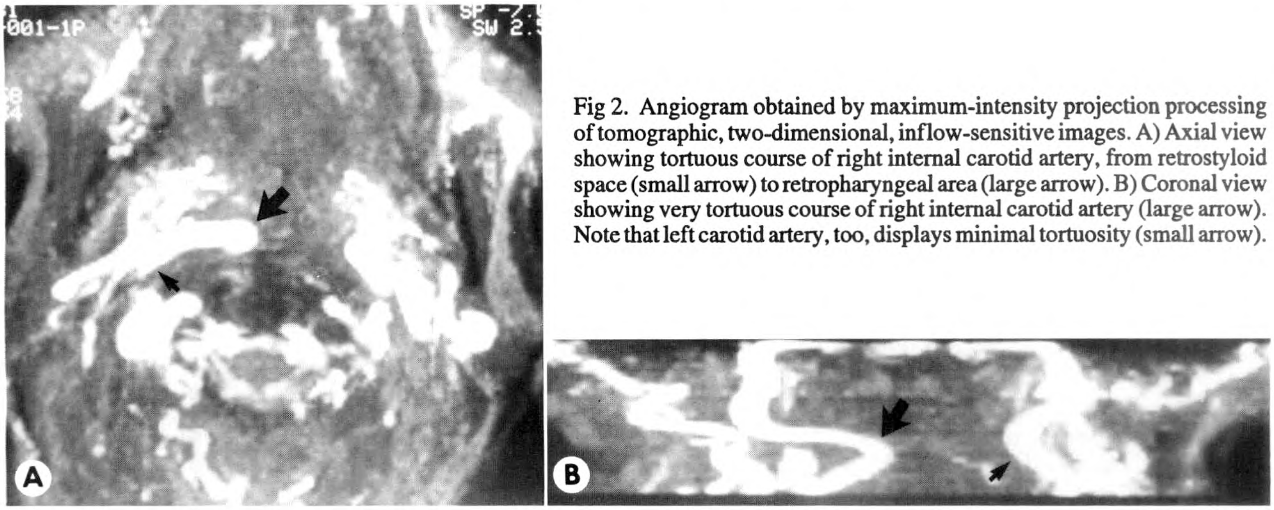

Fig 2. Angiogram obtained by maximum-intensity projection processing of tomographic, two-dimensional, inflow-sensitive images. A) Axial view showing tortuous course of right internal carotid artery, from retrostyloid space (small arrow) to retropharyngeal area (large arrow). B) Coronal view showing very tortuous course of right internal carotid artery (large arrow). Note that left carotid artery, too, displays minimal tortuosity (small arrow).

of the existence of this anomaly, a potential cause of dramatic bleeding during tonsillectomy or adenoidectomy.

McKenzie and Woolf[2] report the case of an injury of the ICA during adenoidectomy. After multiple unsuccessful procedures, the bleeding could only be stopped by ligature of the common carotid artery, and the patient recovered uneventfully. We found three similar cases of bleeding in the literature,[3-5] and the outcome was fatal for two of the patients.[4,5] Bleeding from a tortuous carotid artery during tonsillectomy seems to be more frequent.[6]

The diagnosis of a vascular mass should also be considered in the presence of a suspected peritonsillar, lateropharyngeal, or retropharyngeal abscess. Puncture with a fine needle before blade incision can prevent a dramatic outcome.

When a tortuous ICA is suspected clinically, visualization of the neck great vessels is required to confirm the diagnosis. Conventional angiography is the method of choice, but necessitates the puncture of a big artery, its catheterization, and contrast product injection. It is mainly indicated if a surgical procedure is considered — for example, in the case of a symptomatic kinked vessel.[1] Computed tomography can also facilitate the diagnosis — here, too, requiring the injection of a contrast agent.

Magnetic resonance angiography is a new technique that permits visualization of the major arteries. Because of inferior spatial resolution, it is less accurate than classic angiography, but has the advantage of being noninvasive. Technically, magnetic resonance imaging pulse sequences can be tailored to enhance vascular flow without the need for contrast agents, by using two flow phenomena: time of flight and phase. Time of flight flow-sensitive magnetic resonance imaging yields high signal-to-noise ratios and is simple to implement; it obviates the need for diagnostic angiography in most head and neck masses.[7] Moreover, it is part of an imaging study that exquisitely demonstrates soft tissue masses, and is therefore very useful in further evaluating the relationships of head and neck masses to adjacent great vessels.

CONCLUSION

Awareness of the existence of a possible tortuous ICA is mandatory to avoid serious complications during tonsillectomy, adenoidectomy, incision of peritonsillar or retropharyngeal abscess, or any surgical procedure of the throat. The diagnosis, although clinically suspected, must be confirmed radiographically. Magnetic resonance angiography provides a noninvasive imaging tool that allows diagnosis without vessel catheterization and without contrast product injection. This is especially helpful in patients with atherosclerotic vessels, who moreover are prone to have such a vessel anomaly.

ACKNOWLEDGMENTS — We thank Prof J. M. Gomori and S. Yaffe for their help.

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PATHOLOGY CONSULTATION

EXTRACRANIAL, EXTRASPINAL MENINGIOMAS OF THE HEAD AND NECK

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The head and neck is the most frequent location for extraneuraxial meningiomas, be they wholly extracranial or extraspinal or extensions of central nervous system meningiomas. Regardless of anatomic site of origin, nearly all meningiomas arise from meningocytes of arachnoid granulations. Ectopic arachnoid cell clusters have a predilection for areas of dural penetration of cranial nerves, and it is in these areas that most extracranial meningiomas are found. Surgical excision is the mainstay of treatment and must be planned by radiologic studies to determine the extent of the tumor and the presence or absence of a companion central nervous system meningioma. The often locally invasive and aggressive behavior of the meningiomas belies their benign histologic appearance.

Primary extracranial or extraspinal meningiomas can be defined as those not associated with an underlying meningioma of the neuraxis. Because they are rarely occurring lesions, one must always first consider and exclude an extension from a central meningioma.

Meningiomas in an extracranial or extraspinal site constitute fewer than 2% of all meningiomas and are found most often in the head and neck, with the most common locations being the orbit, the vicinity of the ears, and the skin near the vertebral column.[1] Other head and neck sites are the bones of the skull, the scalp, the soft tissues of the face and neck, the parapharyngeal space, the sinonasal tract, and the middle ear.[2] Oral cavity meningiomas are medical curiosities. The majority of these "ectopic" meningiomas are extensions from primary neuraxial meningiomas along vessels or cranial nerves emerging through the skull's base, or originate from ectopic nests of arachnoid cells. Rarely, the tumors have no demonstrable connection with foramina or cranial nerves. Even more unusual, the extraneuraxial location is a metastasis from a malignant meningioma.

The meninges (pia, arachnoid dura) are derived from embryonic prechordal plate mesenchyme, mesoderm, and neural crest derivatives. Meningiomas arise from meningocytes (arachnoid cap cells) of arachnoid granulation tissue. Ectopic arachnoid cell clusters have a predilection for areas of dural penetrations by cranial nerves I, III, VII, IX, X, XI, and XII, and it is there that most of the extracranial meningiomas are considered to arise. The optic nerve exists at the lamina cribrosa of the ocular globe; hence, most orbital meningiomas are within the central nervous system, but often present extracranially. Table 1 summarizes the several histogenetic sources for primary extracranial meningiomas.

MENINGIOMAS OF TEMPORAL BONE AND MIDDLE EAR

The anterior and posterior surfaces of the temporal bone account for up to 7% of all intracranial meningiomas, and yet extensions into the temporal bone are unusual, and an origin within the temporal bone is rare. Even before advanced radiologic technology, it was estimated that nearly 75% of meningiomas involving the temporal bone were combined intracranial and intra-temporal bone tumors.[3] For the remainder, an extracranial origin was postulated, but that is clearly overstated.

The possible progenitors for primary extracranial temporal bone meningiomas are arachnoid cells located within 1) the internal auditory canal, adjacent to the cochlea and vestibular and facial nerves, as far as

TABLE 1. PROPOSED ORIGINS OF PRIMARY EXTRACRANIAL MENINGIOMAS

Dislocated or entrapped meningocytes during closure of midline structures during intrauterine life (fusion line inclusions)
Meningocytes found around skull's or intervertebral foramina or along perineural sheaths of cranial nerves
Differentiation of Schwann cells into meningocytes
Pluripotential mesenchyme

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TABLE 2. CUTANEOUS MENINGIOMAS

Classification	*Clinicopathologic Features*
Primary cutaneous (type I)	Generally present since birth, with diagnosis in childhood or young adulthood Principally located in scalp, particularly in occiput or along suture lines, forehead, or nose, or periorbital or paravertebral May have bone sinus tract or obliterated stalk connection to central nervous system Same anatomic distribution as meningoceles
Soft tissue and skin (type II)	Can occur at any age, but most common in adults Involves skin by contiguity Located in vicinity of sensory organs (periauricular and perinasal) and scalp, eg, orbital, aural, nasal, buccal, and in approximate distribution of cranial and spinal nerves
Central nervous system and skin (type III)	Represents extension in cutis or subcutis from central nervous system meningioma, eg, direct invasion, via surgical or traumatic defect, "seeding," or metastasis

Prepared from data presented by Lopez et al.[15]

the geniculate ganglion, 2) within the jugular foramen, near the jugular bulb, 3) along the groove of the greater petrosal nerve, along the roof of the eustachian tube, and 4) in small herniations of brain through the tegmen tympani.[4] The middle ear itself is a rare location.[2,3] In the 20 patients with apparent intratympanic meningiomas reviewed by Rietz et al,[3] the initially proposed sites of origin were 45% in the middle ear, 30% in the facial nerve, 10% each in the internal auditory canal and eustachian tube, and 5% in the jugular fossa. Most intratympanic meningiomas are not, however, confined to their anatomic location, but extend into or from within the cranium.[5] It is now clear that there is often an inapparent spread of the tumor through osseous haversian canals, neural foramina, and marrow cells. The failure of earlier imaging techniques to detect this often insidious growth, short follow-up periods, and the relatively silent clinical nature all have contributed to misconceptions regarding intratympanic meningiomas.[6]

Most meningiomas do not involve the internal auditory canal, or do so only to a minor degree. It is also rare to have a meningioma arise from and be confined within the internal auditory canal.[7] Meningiomas that extensively involve the canal have a considerable tendency to invade the inner ear and deep parts of the temporal bone via the lateral end of the canal.[7]

ENCEPHALOCELES OF MIDDLE EAR AND MASTOID

Herniation of brain (encephalocele) into the middle ear and mastoid is usually devoid of arachnoid granulation tissue, but the latter may play a role in the herniation in some instances. The encephaloceles are either acquired (iatrogenic or postinflammatory) or idiopathic (spontaneous).[8,9] In either form, defects of bone or dura are prerequisites. In 1989, Iurato et al[8] indicated that of 139 cases reported in the world literature during the preceding 40 years, 82 (59%) occurred as a postoperative complication of mastoid surgery. Twelve (8.6%) followed nonsurgically treated chronic otitis media or mastoiditis. A like number were posttraumatic, and in 29 (20.9%) the reason for the herniation was deemed idiopathic.

A soft, pulsating mass protruding into the radical cavity through the tegmen is seen in the postoperative cases. This is accompanied by an aural discharge of cerebrospinal fluid (CSF). A CSF otorrhea, a mass in the middle ear, and recurrent meningitis are also seen in the nonoperated and idiopathic forms. Deceptively, one of the more frequent clinical presentations of idiopathic herniation mimics a recurrent serous otitis media.

It is likely that the high rate of tegmen dehiscence (21%) found in skulls examined in unselected necropsies is responsible for the majority of the spontaneous herniations reported, since most of them have expanded through tegmen defects.[10] Protrusions through a posterior fossa bony plate dehiscence also occur.

The herniated brain tissue is histologically not unlike sinonasal encephaloceles and usually does not have a dural or arachnoid sheath. It is composed of mature neural tissue that frequently shows a microglial proliferation in an incompletely enveloping, condensed fibrovascular stroma.

MENINGIOMAS OF SINONASAL TRACT

Although the information is from authors writing without the benefit of advanced radiologic techniques, it is claimed that intracranial meningiomas only occasionally extend into the upper respiratory tract.[11,12] Nearly 19% (71/371) of intracranial meningiomas reported by Farr et al[13] in 1970 also involved the nasal cavity, paranasal sinuses, or nasopharynx. Taxy[12] believes that most meningiomas in these regions are primary extracranial tumors. He further

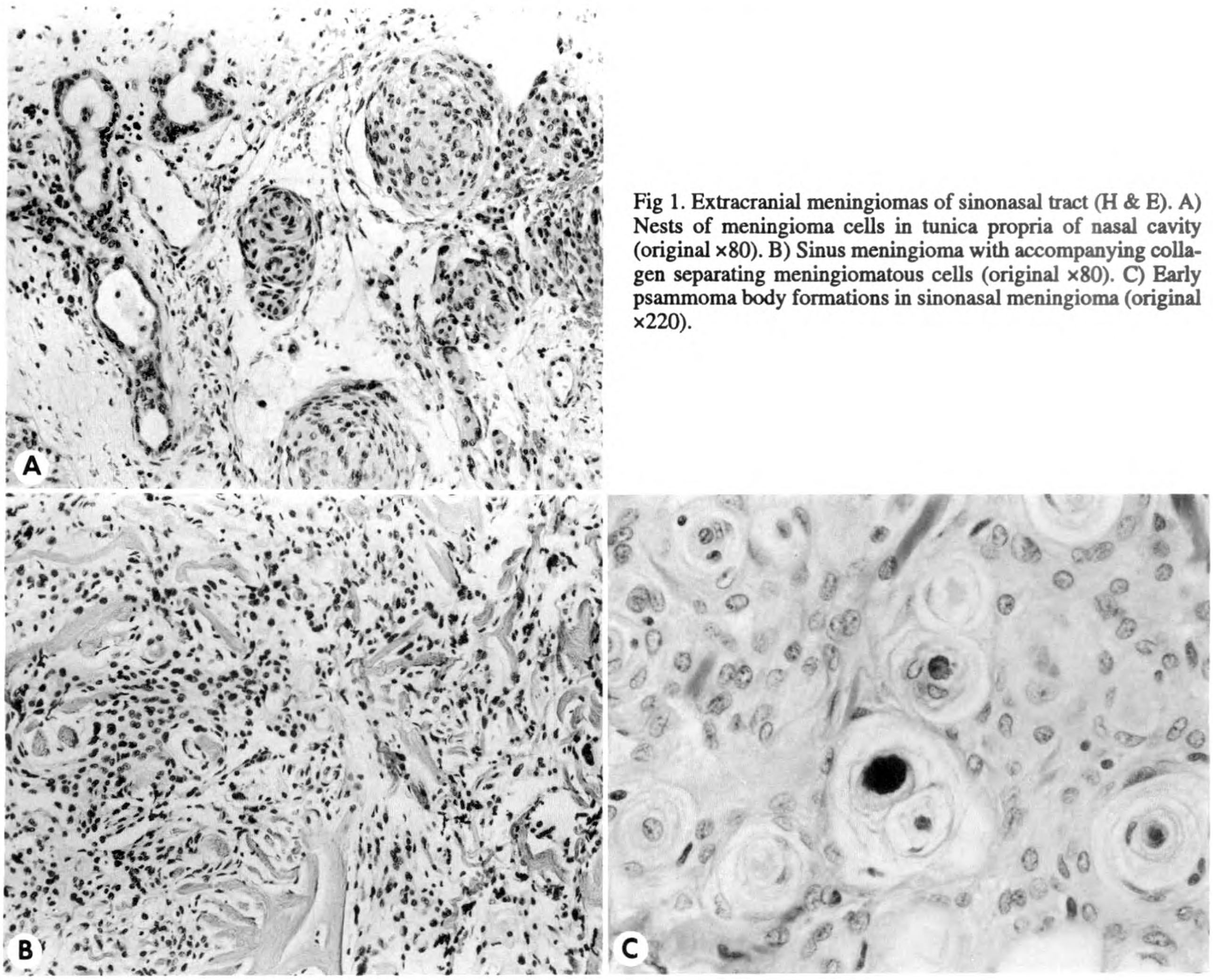

Fig 1. Extracranial meningiomas of sinonasal tract (H & E). A) Nests of meningioma cells in tunica propria of nasal cavity (original ×80). B) Sinus meningioma with accompanying collagen separating meningiomatous cells (original ×80). C) Early psammoma body formations in sinonasal meningioma (original ×220).

reports that in 30 cases of sinonasal meningiomas, the nasal cavity was involved in 14, the frontal and maxillary sinuses in 8, the sphenoid in 7, and the ethmoid sinuses in 8. Irving et al[14] indicate that 6 of their tumors were confined to the maxillary antrum. Extensive involvement can produce exophthalmos, proptosis, ptosis, orbital deviation, and other ocular signs, as well as facial deformity. Smaller lesions can simulate nasal polyps or other intranasal masses. Sclerosis or destruction of bone at the base of the skull may indicate an intracranial primary.

CUTANEOUS MENINGIOMAS

The most complete analysis of meningiomas involving the skin is that of Lopez et al.[15] Table 2[15] is a synopsis of their findings and underscores the fact that the majority of cutaneous meningiomas involve the head and neck. Clinically, cutaneous meningiomas resemble a variety of skin lesions ranging from skin tags and epidermal inclusion cysts to invasive soft tissue neoplasms. Although the histologic appearance of cutaneous meningiomas may deviate somewhat from that of classic intracranial types of meningioma, we do not consider the rare "meningioma-like tumor of the skin" (an immature fibrohistiocytic or possibly nerve sheath neoplasm with great similarity to the canine hemangiopericytoma)[16] to pose a problem in differential diagnosis. Their predilection for acral locations also serves as a distinguishing feature.

Histologically, meningiomas in extracranial locations do not differ substantially from their neuraxial counterparts. Four microscopic patterns dominate: 1) syncytial, characterized by uniform sheets of polygonal cells, 2) transitional or psammomatous, with a whorled pattern of polygonal or spindle cells and varying numbers of psammoma bodies, 3) fibrous, manifesting an increase in collagenous tissue and a corresponding decrease of cellularity, and 4) angioblastic and hemangiopericytomalike. In our experience, the extracranial meningiomas are most often of the transitional or syncytial forms (Fig 1). Cells of meningiomas are immunoreactive for S-100 protein antigen, vimentin, keratin, and epithelial membrane antigen. Electron optic features include complex interdigitations of cellular plasma membranes, many

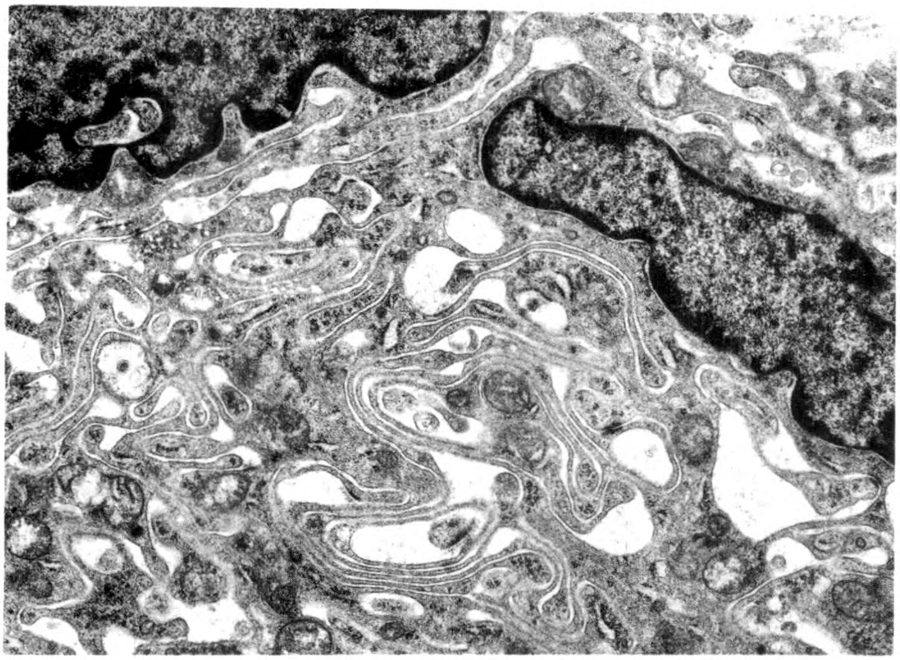

Fig 2. Electron photomicrograph of extracranial meningioma in neck. Note complex interdigitations and cytoplasmic filaments.

desmosomes, and bundles of intermediate filaments (Fig 2).

Irrespective of a benign histologic appearance, extracranial meningiomas may manifest extensive invasive properties, even to intravascular extension.[17] We know of no histologically malignant extracranial meningioma with metastasis. A patient (case 6) reported by Granich et al[2] developed spread to the lungs without histologic criteria for malignancy in the meningioma or the pulmonary nodules.

Surgical excision, often with intracranial techniques, is the treatment of choice. State-of-the-art imaging techniques are essential for defining the extent of the tumors.

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LETTERS TO THE EDITOR

To the Editor:

I read with interest the excellent series and review by Koltai and Quiney (Tracheal Agenesis, *Ann Otol Rhinol Laryngol* 1992;101:560-6) concerning the extremely rare congenital anomaly of tracheal agenesis (TA). I wish to present another case (case number 53), in which I performed the postmortem examination, and discuss various aspects of this case related to the current literature.[1-7]

A male infant was born by vaginal delivery at 32 weeks of gestational age (1,560 g) in Florence, SC, to a 17-year-old gravida 1, para 0, aborta 0 woman. At birth the infant was cyanotic, bradycardic, and unable to cry. His Apgar scores were 4 (1 minute), 5 (5 minutes), and 8 (10 minutes). Tracheal intubation was unsuccessfully attempted; however, intubation was successful through the esophagus. The infant was immediately transferred to the Medical University of South Carolina Pediatric Surgery Division, where endoscopy revealed TA and a tracheoesophageal fistula emanating from the distal esophagus that correlated with radiologic studies. Continued mechanical support through the esophagus maintained vital functions; however, because the anomaly could not be medically or surgically corrected, the infant was weaned off the ventilator and died a short time later.

At postmortem examination, TA with a blind subglottic pouch and a carina (ostia 0.1 cm in diameter) arising from the distal esophagus 6.4 cm from the inferior aspect of the epiglottis was evident (Floyd's type II). In addition, there was constriction of the esophagus distal to the tracheoesophageal fistula, a Meckel's diverticulum 0.7 cm in length by 0.3 cm in width, a complete second-segment duodenal membranous web (atresia) proximal to the ampulla of Vater, and a 1.3 x 1.0 x 0.7-cm triangular additional lobe emanating from the anterior-superior aspect of the right liver lobe.

As with the 5 cases presented by Koltai and Quiney, this case has features more applicable to the recently introduced TACRD association/syndrome,[1,2] (laryngotracheal atresia, complex congenital cardiac abnormalities, radial ray defects, and duodenal atresia) than either the VATER or VACTERL associations/syndromes.[3-6] Both VATER (vertebral defects, anal atresia, tracheoesophageal fistula and/or esophageal atresia, radial dysplasia, renal defects) and VACTERL (VATER plus cardiovascular and limb defects) associations/syndromes list esophageal atresia as a component; however, in this case there was only esophageal constriction. In addition, prematurity and Meckel's diverticulum[1,2] (occurring in 12.9% of previously reported cases) appear to be common characteristics of infants with TA. An interesting finding was the additional anterior-superior liver lobe — unusual, since additional liver lobes, rare in themselves, characteristically arise from the inferior surface.[8] Effman et al[7] in 1975 described a case of TA with unspecified "minor form anomalies of liver," and Diaz et al[2] in 1989 listed a case of "hepatomegaly" discovered in their review of the literature.

Review of the current literature concerning the 52 previously reported cases of TA reveals a wide variety of associated congenital anomalies.[1-7] However, the application of formal associations/syndromes such as TACRD, VATER, and VACTERL has significant implications for the afflicted infant, clinician, and parents concerning the genetic causation, evaluation, prognosis, counseling, and fate of the newborn. Therefore, it is important to report cases of TA and obtain a detailed autopsy so that all associated anomalies, both apparent and silent, may be discovered, enabling a statistically relevant understanding of TA. This approach is especially significant if neck exploration and surgical correction, either by anatomic rearrangement or prostheses, is to be attempted on a regular basis in the future for an anomaly that is currently uniformly fatal.

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BOOK REVIEWS

Surgery of Cranial Base Tumors

Laligam N. Sekhar and Ivo P. Janecka, editors. Hard cover, illustrated, indexed, 870 pages, 1993. Raven Press, New York, NY.

With their 68 colleagues, the editors present the first atlas of surgical removal of cranial base tumors. The voluminous illustrations (most in color) are accompanied by more written text than is usual for an atlas, which adds to its importance as a teaching and reference book.

Divided into 6 sections (54 chapters), this book essentially only deals with surgical removal of cranial base tumors. Developmental lesions (basal encephaloceles, craniosynostosis), complex skull base trauma, and vascular lesions (aneurysms, atrioventricular malformations) occurring in the temporal bone, however, are addressed in the first section, in which general cranial base surgical principles and techniques are discussed. Also covered in the 8 chapters of this section are the general principles of magnetic resonance imaging and computed tomography evaluations, arteriography, balloon occlusion testing of the internal carotid artery, embolization techniques, cerebral revascularization, and neurophysiologic monitoring during tumor removal.

Professor Johannes Lang of Würzburg, the author of several texts on surgical anatomy of the cranial base, is the sole author of the 3 chapters in the second section of this book. His discussions include the anterior and middle cranial fossae (including the cavernous sinus and orbit), anatomy of the paranasal sinuses, and anatomy of the posterior cranial fossa.

Surgical approaches (subtemporal, infratemporal, extended, frontal, transoral, transmaxillary, facial translocation, and extreme transcondylar) are presented by the authors of the 15 chapters in this book's third section. This is the section that will intrigue the otolaryngologist the most. Many of these authors have chosen the typical format of an introductory discussion of the indications for surgery, preoperative evaluations, and avenues for monitoring treatments. Although reasonably comprehensive in scope, some points are too briefly discussed. For example, an en bloc resection of the temporal bone could not be carried out by following the ambiguous anatomic descriptions given, such as "over the temporal lobe," and "A neural incision is made at the junction with the middle fossa." Such is not the case throughout this section, however. In describing translabyrinthine-transcochlear approaches, for example, the procedure is clearly defined: "The dura of the posterior fossa is then incised over the midportion of the internal auditory canal. The incision then extends around the porus acusticus superiorly and inferiorly. Care is taken to avoid vessels on the surface of the tumor and anteriorly/superiorly care is exercised to avoid injury to the facial nerve, which lies directly beneath the dura in this area." Given such distinct details, a surgeon could proceed with the surgery by following the anatomic descriptions.

In the 5 chapters in the fourth section, cranial base reconstruction (regional flaps, microvascular flaps, facial nerve reanimation techniques, and the use of alloplastic material) is discussed in detail. Specific tumors are addressed in the fifth section (20 chapters). These include esthesioneuroblastomas, juvenile angiofibromas, petroclival meningiomas, clivus chordomas, and others. The last 3 chapters of this book make up the sixth section, which deals with rehabilitation and complications following skull base surgery.

Inevitably, continuity suffers when there are a large number of contributors to a text, especially if they come from a wide area of the world. One example in this text is represented by the excellent drawings of Jon Coulter, which are noticeably confined to a specific area. The quality of the photomicrographs also appears to differ, with those depicting neurosurgery seeming to have greater depth of field than do those depicting otologic surgery. Nevertheless, the editors have prepared a wealth of information, well documented by a myriad of color illustrations, schematic drawings, and computed tomographic and magnetic resonance images. Although this is an excellent reference book for otologists, otolaryngologists, neurosurgeons, and others who deal with cranial base surgery patients, alone it is not consummate, but rather, a significant aid in learning about surgery for cranial base tumors.

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Pediatric Sinusitis

Rodney P. Lusk, editor. Hard cover, illustrated, indexed, 149 pages, 1992. Raven Press, New York, NY, $125.

With few exceptions, the 13 authors included in this book are affiliated with Washington University School of Medicine or St Louis Children's Hospital in Missouri. It is organized by 11 topics covering signs and symptoms, pathophysiology, imaging, microbiology, allergy, immune deficiency, asthma, cystic fibrosis, medical management, surgery, and complications — all as related to sinusitis in children. The text, which is presented in a concise format, is informative, easy to read, and amply augmented by feature boldfaced headings, line drawings, tables, and color photographs to present all information relevant to that topic. The extensive chapter on imaging is augmented with photographic samples of plain radiographs, computed tomography, and magnetic resonance imaging.

There is clearly a hierarchy of therapeutic options presented. Barely touched are the differences in sinusitis in adults versus in children, and the use of corticosteroid sprays. How common is the need for surgery in cases of pediatric sinusitis; or are criteria for that yet to be achieved? The reader may get the impression that much of what is known about pediatric sinusitis is based on reports of the disease in adults.

One of the book's strongest features is the ease with which the reader can identify information regarding symptoms characteristic of pediatric sinusitis and bacteria that commonly cause the disease. The references are up-to-date and the text presents current knowledge on the subject.

Depending on their interest, specialists will find various sections of the book useful. The primary-care physician and pediatrician should find the more medically oriented chapters helpful. The chapters on surgery and complications should be worthwhile to the otolaryngologist. The atlas-like color photographs provide excellent information for nurses and patients.

Since surgery on the sinuses in children cannot be performed safely without an extensive knowledge of anatomy of the pediatric nose, it is recommended that the physician contemplating such procedures make an intensive study of that structure. This book would advance, but not completely fulfill, that pursuit.

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